10/200125

## SEQUENCE LISTING AP20 RESCREWING 12 MAY 2006

- <110> James, David Cooney, Gregory J Molero-Navajas, Juan C
- <120> Methods of validating target for modulating insulin action, screening for modulators of insulin action and therapeutic uses thereof
- <130> 42-000500US
- <150> AU 2003906286
- <151> 2003-11-14
- <150> PCT/AU2004/001572
- <151> 2004-11-15
- <150> AU 2003906285
- <151> 2003-11-14
- <160> 268
- <170> PatentIn version 3.3
- <210> 1
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- Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp Lys Val 50 55 60
- Val Arg Leu Cys Gln Asn Pro Asn Val Ala Leu Lys Asn Ser Pro Pro 65 70 75 80
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Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn Glu Tyr

100 105 110

Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln Thr Ile 115 120 125

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Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp Lys Val 50 55 60

Val Arg Leu Cys Gln Asn Pro Asn Val Ala Leu Lys Asn Ser Pro Pro 65 70 75 80

Tyr Ile Leu Asp Leu Leu Pro Asp Thr Tyr Gln His Leu Arg Thr Val 85 90 95

Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn Glu Tyr 100 105 110

Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln Thr Ile 115 120 125

Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn Ser Gln 130 135 140

Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala Leu His Glu Val His Pro Ile Ser Ser Gly Leu Glu Ala Met Ala Leu Lys Ser Thr Ile Asp Leu Thr Cys Asn Asp Tyr Ile Ser Val Phe Glu Phe Asp Ile Phe Thr Arg Leu Phe Gln Pro Trp Ser Ser Leu Leu Arg Asn Trp Asn Ser Leu Ala Val Thr His Pro Gly Tyr Met Ala Phe Leu Thr Tyr Asp Glu Val Lys Ala Arg Leu Gln Lys Phe Ile His Lys Pro Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Ile Cys Ala Glu Asn 

Asp Lys Asp Val Lys Ile Glu Pro Cys Gly His Leu Met Cys Thr Ser Cys Leu Thr Ser Trp Gln Glu Ser Glu Gly Gln Gly Cys Pro Phe Cys Arg Cys Glu Ile Lys Gly Thr Glu Pro Ile Val Val Asp Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Glu Arg Ala Asp Asp Ser Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg Pro Ser Ser Pro Phe Ser Met Ala Pro Gln Ala Ser Leu Pro Pro Val Pro Pro Arg Leu Asp Leu Leu Gln Gln Arg Ala Pro Val Pro Ala Ser Thr Ser Val Leu Gly Thr Ala Ser Lys Ala Ala Ser Gly Ser Leu His Lys Asp Lys Pro Leu Pro Ile Pro Pro Thr Leu Arg Asp Leu Pro Pro Pro Pro Pro Pro Asp Arg Pro Tyr Ser Val Gly Ala Glu Thr Arg Pro Gln Arg Arg Pro Leu Pro Cys Thr Pro Gly Asp Cys Pro Ser Arg Asp Lys Leu Pro Pro Val Pro Ser Ser Arg Pro Gly Asp Ser Trp Leu Ser Arg Thr Ile Pro Lys Val Pro Val Ala Thr Pro Asn Pro Gly Asp Pro Trp Asn Gly Arg Glu Leu Thr Asn Arg His Ser Leu Pro Phe Ser Leu Pro Ser Gln 595 600 605

Met Glu Pro Arg Ala Asp Val Pro Arg Leu Gly Ser Thr Phe Ser Leu Asp Thr Ser Met Thr Met Asn Ser Ser Pro Val Ala Gly Pro Glu Ser Glu His Pro Lys Ile Lys Pro Ser Ser Ser Ala Asn Ala Ile Tyr Ser Leu Ala Ala Arg Pro Leu Pro Met Pro Lys Leu Pro Pro Gly Glu Gln Gly Glu Ser Glu Glu Asp Thr Glu Tyr Met Thr Pro Thr Ser Arg Pro Val Gly Val Gln Lys Pro Glu Pro Lys Arg Pro Leu Glu Ala Thr Gln Ser Ser Arg Ala Cys Asp Cys Asp Gln Gln Ile Asp Ser Cys Thr Tyr Glu Ala Met Tyr Thr Ile Gln Ser Gln Ala Leu Ser Val Ala Glu Asn Ser Ala Ser Gly Glu Gly Asn Leu Ala Thr Ala His Thr Ser Thr Gly Pro Glu Glu Ser Glu Asn Glu Asp Asp Gly Tyr Asp Val Pro Lys Pro Pro Val Pro Ala Val Leu Ala Arg Arg Thr Leu Ser Asp Ile Ser Asn Ala Ser Ser Ser Phe Gly Trp Leu Ser Leu Asp Gly Asp Pro Thr Asn Phe Asn Glu Gly Ser Gln Val Pro Glu Arg Pro Pro Lys Pro Phe Pro Arg Arg Ile Asn Ser Glu Arg Lys Ala Ser Ser Tyr Gln Gln Gly Gly 

Gly Ala Thr Ala Asn Pro Val Ala Thr Ala Pro Ser Pro Gln Leu Ser 835 840 845

Ser Glu Ile Glu Arg Leu Met Ser Gln Gly Tyr Ser Tyr Gln Asp Ile 850 855 860

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Phe Gln Pro His His His His His His Leu Ser Pro His Pro Pro 35 40 45

Gly Thr Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp 50 . 55 60

Lys Val Val Arg Leu Cys Gln Asn Pro Lys Leu Ala Leu Lys Asn Ser 65 70 75 80

Pro Pro Tyr Ile Leu Asp Leu Leu Pro Asp Thr Tyr Gln His Leu Arg 85 90 95

Thr Ile Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn 100 105 110

Glu Tyr Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln 115 120 125

Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala Leu His Glu Val His Pro Ile Ser Ser Gly Leu Glu Ala Met Ala Leu Lys Ser Thr Ile Asp Leu Thr Cys Asn Asp Tyr Ile Ser Val Phe Glu Phe Asp Ile Phe Thr Arg Leu Phe Gln Pro Trp Ser Ser Leu Leu Arg Asn Trp Asn Ser Leu Ala Val Thr His Pro Gly Tyr Met Ala Phe Leu Thr Tyr Asp Glu Val Lys Ala Arg Leu Gln Lys Phe Ile His Lys Pro Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Glu Gln Tyr

Glu Leu Tyr Cys Glu Met Gly Ser Thr Phe Gln Leu Cys Lys Ile Cys Ala Glu Asn Asp Lys Asp Val Lys Ile Glu Pro Cys Gly His Leu Met Cys Thr Ser Cys Leu Thr Ser Trp Gln Glu Ser Glu Gly Gln Gly Cys Pro Phe Cys Arg Cys Glu Ile Lys Gly Thr Glu Pro Ile Val Val Asp Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Glu Arg Ala Asp Asp Thr Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg Pro Pro Ser Pro Phe Ser Met Ala Pro Gln Ala Ser Leu Pro Pro Val Pro Pro Arg Leu Asp Leu Leu Pro Gln Arg Val Cys Val Pro Ser Ser Ala Ser Ala Leu Gly Thr Ala Ser Lys Ala Ala Ser Gly Ser Leu His Lys Asp Lys Pro Leu Pro Val Pro Pro Thr Leu Arg Asp Leu Pro Pro Pro Pro Pro Pro Asp Arg Pro Tyr Ser Val Gly Ala Glu Ser Arg Pro Gln Arg Arg Pro Leu Pro Cys Thr Pro Gly Asp Cys Pro Ser Arg Asp Lys Leu Pro Pro Val Pro Ser Ser Arg Leu Gly Asp Ser Trp Leu Pro 

Arg Pro Ile Pro Lys Val Pro Val Ser Ala Pro Ser Ser Ser Asp Pro Trp Thr Gly Arg Glu Leu Thr Asn Arg His Ser Leu Pro Phe Ser Leu Pro Ser Gln Met Glu Pro Arg Pro Asp Val Pro Arg Leu Gly Ser Thr Phe Ser Leu Asp Thr Ser Met Ser Met Asn Ser Ser Pro Leu Val Gly Pro Glu Cys Asp His Pro Lys Ile Lys Pro Ser Ser Ala Asn Ala Ile Tyr Ser Leu Ala Ala Arg Pro Leu Pro Val Pro Lys Leu Pro Pro Gly Glu Gln Cys Glu Gly Glu Glu Asp Thr Glu Tyr Met Thr Pro Ser Ser Arg Pro Leu Arg Pro Leu Asp Thr Ser Gln Ser Ser Arg Ala Cys Asp Cys Asp Gln Gln Ile Asp Ser Cys Thr Tyr Glu Ala Met Tyr Asn Ile Gln Ser Gln Ala Pro Ser Ile Thr Glu Ser Ser Thr Phe Gly Glu Gly Asn Leu Ala Ala Ala His Ala Asn Thr Gly Pro Glu Glu Ser Glu Asn Glu Asp Asp Gly Tyr Asp Val Pro Lys Pro Pro Val Pro Ala Val . 775 Leu Ala Arg Arg Thr Leu Ser Asp Ile Ser Asn Ala Ser Ser Ser Phe Gly Trp Leu Ser Leu Asp Gly Asp Pro Thr Thr Asn Val Thr Glu Gly 

Ser Gln Val Pro Glu Arg Pro Pro Lys Pro Phe Pro Arg Arg Ile Asn 820 825 830

Ser Glu Arg Lys Ala Gly Ser Cys Gln Gln Gly Ser Gly Pro Ala Ala 835 840 845

Ser Ala Ala Thr Ala Ser Pro Gln Leu Ser Ser Glu Ile Glu Asn Leu 850 855 860

Met Ser Gln Gly Tyr Ser Tyr Gln Asp Ile Gln Lys Ala Leu Val Ile 865 870 875 880

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Pro Ala Ser Asp Asn Ser Gly Glu Thr Pro Gln Arg Asn Gly Glu Gly 50 55 60

His Thr Leu His Lys Asp Thr Gln Pro Gly Arg Ala Gln Pro Pro Thr 65 70 . 75 80

Lys Ala Gln Arg Ser Gly Arg Arg Arg Asn Ser Leu Pro Pro Ser Arg 85 90 95

Gln Lys Pro Pro Arg Asn Pro Leu Ser Ser Ser Asp Ala Ala Pro Ser

| Pro        | Glu        | Leu<br>115 | Gln        | Ala        | Asn        | Gly        | Thr<br>120 | Gly        | Thr        | Gln        | Gly        | Leu<br>125 | Glu        | Ala        | Thr        |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Asp        | Thr<br>130 | Asn        | Gly        | Leu        | Ser        | Ser<br>135 | Ser        | Ala        | Arg        | Pro        | Gln<br>140 | Gly        | Ser        | Lys        | Leu        |
| Val<br>145 | Pro        | Ser        | Lys        | Glu        | Asp<br>150 | Lys        | Lys        | Gln        | Ala        | Asn<br>155 | Ile        | Lys        | Arg        | Gln        | Leu<br>160 |
| Met        | Thr        | Asn        | Phe        | Ile<br>165 | Leu        | Gly        | Ser        | Phe        | Asp<br>170 | Asp        | Tyr        | Ser        | Ser        | Asp<br>175 | Glu        |
| Asp        | Ser        | Val        | Ala<br>180 | Gly        | Ser        | Ser        | Arg        | Glu<br>185 | Ser        | Thr        | Arg        | Lys        | Gly<br>190 | Ser        | Arg        |
| Ala        | Ser        | Leu<br>195 | Gly        | Ala        | Leu        | Ser        | Leu<br>200 | Glu        | Ala        | Tyr        | Leu        | Thr<br>205 | Thr        | Gly        | Glu        |
| Ala        | Glu<br>210 | Thr        | Arg        | Val        | Pro        | Thr<br>215 | Met        | Arg        | Pro        | Ser        | Met<br>220 | Ser        | Gly        | Leu        | His        |
| Leu<br>225 | Val        | Lys        | Arg        | Gly        | Arg<br>230 | Glu        | His        | Lys        | Lys        | Leu<br>235 | Asp        | Leu        | His        | Arg        | Asp<br>240 |
| Phe        | Thr        | Val        | Ala        | Ser<br>245 | Pro        | Ala        | Glu        | Phe        | Val<br>250 | Thr        | Arg        | Phe        | Gly        | Gly<br>255 | Asp        |
| Arg        | Val        | Ile        | Glu<br>260 | Lys        | Val        | Leu        | Ile        | Ala<br>265 | Asn        | Asn        | Gly        | Ile        | Ala<br>270 | Ala        | Val        |
| Lys        | Cys        | Met<br>275 | Arg        | Ser        | Ile        | Arg        | Arg<br>280 | Trp        | Ala        | Tyr        | Glu        | Met<br>285 | Phe        | Arg        | Asr        |
| Glu        | Arg<br>290 | Ala        | Ile        | Arg        | Phe        | Val<br>295 | Arg        | Met        | Val        | Thr        | Pro<br>300 | Glu        | Asp        | Leu        | Lys        |
| Ala<br>305 | Asn        | Ala        | Glu        | Tyr        | Ile<br>310 | Lys        | Met        | Ala        | Asp        | His<br>315 | Tyr        | Gly        | Pro        | Ala        | Pro<br>320 |
| Gly        | Gly        | Pro        | Asn        | Asn<br>325 | Asn        | Asn        | Tyr        | Ala        | Asn<br>330 | Val        | Glu        | Leu        | Ile        | Val<br>335 | Asp        |

- Ile Ala Lys Arg Ile Pro Leu Gln Ala Val Trp Ala Gly Trp Gly His 340 345 350
- Ala Leu Glu Asn Pro Lys Leu Pro Glu Leu Leu Cys Lys Asn Gly Val 355 360 365
- Ala Phe Leu Gly Pro Pro Arg Leu Arg Pro Met Val Gly Leu Gly Asp 370 375 380
- Lys Ile Ala Ser Thr Val Val Ala Gln Thr Leu Gln Val Pro Thr Leu 385 390 395 400
- Pro Arg Ser Gly Ser Ala Leu Thr Val Glu Trp Thr Glu Asp Asp Leu 405 410 415
- Gln Gln Gly Lys Arg Ile Ser Val Pro Glu Asp Val Tyr Asp Lys Gly
  420 425 430
- Cys Val Lys Asp Val Asp Glu Gly Leu Glu Ala Ala Glu Arg Ile Gly
  435 440 445
- Phe Pro Leu Met Ile Lys Ala Ser Glu Gly Gly Gly Lys Gly Ile 450 455 460
- Arg Glu Thr Glu Ser Ala Glu Asp Phe Pro Ile Leu Phe Arg Gln Val 465 470 475 480
- Gln Ser Glu Ile Pro Gly Ser Pro Ile Phe Leu Met Lys Leu Ala Gln 485 490 495
- His Ala Arg His Leu Glu Val Gln Ile Leu Ala Asp Gln Tyr Gly Asn 500 505 510
- Ala Val Ser Leu Phe Gly Arg Asp Cys Ser Ile Gln Arg Arg His Gln 515 520 525
- Lys Ile Val Glu Glu Ala Pro Ala Thr Ile Ala Pro Leu Ala Ile Phe 530 540
- Glu Phe Met Glu Gln Cys Ala Ile Arg Leu Ala Lys Thr Val Gly Tyr 545 550 555 560

Val Ser Ala Gly Thr Val Glu Tyr Leu Tyr Ser Gln Asp Gly Ser Phe 565 570 575

His Phe Leu Glu Leu Asn Pro Arg Leu Gln Val Glu His Pro Cys Thr 580 585 590

Glu Met Ile Ala Asp Val Asn Leu Pro Ala Ala Gln Leu Gln Ile Ala 595 600 605

Met Gly Ala Pro Leu His Arg Leu Lys Asp Ile Arg Leu Leu Tyr Gly 610 620

Glu Ser Pro Trp Gly Asp Ser Pro Ile Ser Phe Glu Asn Ser Ala His 625 630 635 640

Leu Pro Cys Pro Arg Gly His Val Ile Ala Thr Arg Ile Thr Ser Glu 645 650 655

Asn Pro Asp Glu Gly Phe Lys Pro Ser Ser Gly Thr Val Gln Glu Leu 660 665 670

Asn Phe Arg Ser Ser Lys Asn Val Trp Gly Tyr Phe Thr Val Ala Ala 675 680 685

Thr Gly Gly Leu His Glu Phe Ala Ile Ser Gln Phe Gly His Cys Phe 690 695 700

Ser Trp Gly Glu Asn Arg Lys Glu Ala Ile Ser Asn Met Val Val Ala 705 710 715 720

Leu Lys Glu Leu Ser Leu Arg Gly Asp Phe Arg Thr Thr Val Glu Tyr .725 730 735

Leu Ile Asn Leu Leu Glu Thr Glu Ser Phe Gln Asn Asn Tyr Ile Asp 740 745 750

Thr Gly Trp Leu Asp Tyr Leu Ile Ala Glu Lys Val Gln Lys Lys Pro
755 760 765

Asn Ile Met Leu Gly Val Val Cys Gly Ala Leu Glu Arg Gly Asp Ala 770 780

Met Phe Arg Thr Cys Met Thr Asp Phe Leu His Ser Leu Glu Arg Gly Gln Val Leu Pro Ala Asp Ser Leu Leu Asn Leu Val Asp Val Glu Leu Ile Tyr Glu Gly Val Lys Tyr Ile Leu Lys Val Thr Arg Gln Ser Leu Thr Met Phe Val Leu Ile Met Asn Gly Cys His Ile Glu Ile Asp Ala His Arg Leu Asn Asp Gly Gly Leu Leu Leu Ser Tyr Asn Gly Asn Ser Tyr Thr Thr Tyr Met Lys Glu Glu Val Asp Ser Tyr Arg Thr Ile Gly Asn Lys Thr Cys Val Phe Glu Lys Glu Asn Asp Pro Thr Val Leu Arg Ser Pro Ser Ala Gly Lys Leu Thr Gln Ile Thr Val Glu Asp Gly Gly His Val Glu Ala Gly Arg Arg Tyr Ala Glu Met Glu Val Met Lys Met Ile Met Thr Leu Asn Val Gln Glu Arg Gly Arg Val Lys Tyr Ile Lys Arg Pro Gly Ala Val Leu Glu Ala Gly Cys Val Val Ala Arg Leu Glu Leu Asp Asp Pro Ser Lys Val His Pro Ala Glu Pro Phe Thr Gly Glu Leu Pro Ala Gln Gln Asn Thr Ala Asp Leu Gly Lys Lys Leu His Arg Val Phe His Ser Val Leu Gly Ser Leu Thr Asn Val Met Ser Gly Phe

Cys Leu Pro Glu Pro Phe Phe Ser Ile Lys Leu Lys Glu Trp Val

1010 1015 1020

| Gln | Lys<br>1025 | Leu | Met | Met | Thr | Leu<br>1030 | Arg | His | Pro | Ser | Leu<br>1035 | Leu | Leu | Asp |
|-----|-------------|-----|-----|-----|-----|-------------|-----|-----|-----|-----|-------------|-----|-----|-----|
| Val | Gln<br>1040 | Glu | Ile | Met |     | Ser<br>1045 | Arg | Ala | Gly | Arg | Ile<br>1050 | Pro | Pro | Pro |
| Val | Glu<br>1055 | Lys | Ser | Val |     | Lys<br>1060 | Val | Met | Ala | Gln | Tyr<br>1065 | Ala | Ser | Asn |
| Ile | Thr<br>1070 |     | Val | Leu |     | Gln<br>1075 |     | Pro | Ser | Gln | Gln<br>1080 |     | Ala | Thr |
| Ile | Leu<br>1085 | Asp | Cys | His | Ala | Ala<br>1090 |     | Leu | Gln | Arg | Lys<br>1095 | Ala | Asp | Arg |
| Glu | Val<br>1100 |     | Phe | Ile | Asn | Thr<br>1105 | Gln | Ser | Met | Val | Gln<br>1110 | Leu | Val | Gln |
| Arg | Tyr<br>1115 |     | Ser | Gly | Ile | Arg<br>1120 |     | His | Met | Lys | Thr<br>1125 | Val | Val | Ile |
| Asp | Leu<br>1130 |     | Arg | Arg | Tyr | Leu<br>1135 |     | Val | Glu | Thr | Ile<br>1140 |     | Gly | Lys |
| Ala | Arg<br>1145 |     | Ala | Asp | Ala | Asn<br>1150 |     | Ser | Gly | Met | Val<br>1155 | Gly | Gly | Val |
| Arg | Ser<br>1160 | Leu | Ser | Phe | Thr | Ser<br>1165 | Val | Trp | Val | Val | Leu<br>1170 | Ser | Pro | Pro |
| Ala | His<br>1175 |     | Asp | Lys | Cys | Val<br>1180 |     | Asn | Leu | Arg | Glu<br>1185 |     | Phe | Lys |
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| Val | Thr<br>1205 |     | Lys | Asn | Gln | Leu<br>1210 | Val | Ile | Met | Leu | Ile<br>1215 |     | Glu | Leu |
| Cys | Gly<br>1220 |     | Asp | Pro | Ser | Leu<br>1225 |     | Asp | Glu | Leu | Ile<br>1230 |     | Ile | Leu |

Asn Glu Leu Thr Gln Leu Ser Lys Ser Glu His Cys Lys Val Ala 1235 1240 1245

Leu Arg Ala Arg Gln Ile Leu Ile Ala Ser Pro Ser Tyr Glu Leu 1250 1255 1260

Arg His Asn Gln Val Glu Ser Ile Phe Leu Ser Ala Ile Asp Met 1265 1270 1275

Tyr Gly His Gln Phe Cys Pro Glu Asn Leu Gln Lys Leu Ile Leu 1280 1285 1290

Ser Glu Thr Thr Ile Phe Asp Val Leu Asn Thr Phe Phe Tyr His 1295 1300 1305

Ala Asn Lys Val Val Cys Met Ala Ser Leu Glu Val Tyr Val Gly 1310 1315 1320

Gly Ala Tyr Ile Ala Tyr Val Leu Asn Ser Leu Gln His Arg Gln 1325 1330 1335

Leu Pro Asp Gly Thr Cys Val Val Glu Phe Gln Phe Met Leu Pro 1340 1345 1350

Ser Ser His Pro Asn Arg Met Thr Val Pro Ile Ser Ile Thr Asn 1355 1360 1365

Pro Asp Leu Leu Arg His Thr Thr Glu Leu Phe Met Asp Ser Gly 1370 1375 1380

Phe Ser Pro Leu Cys Gln Arg Met Gly Ala Met Val Ala Phe Arg 1385 1390 1395

Arg Phe Glu Asp Phe Thr Arg Asn Phe Asp Glu Val Ile Ser Cys 1400 1405 1410

Phe Ala Asn Val Pro Lys Asp Pro Pro Leu Phe Ser Glu Ala Arg 1415 1420 1425

Thr Ser Leu Tyr Ser Glu Asp Asp Cys Lys Ser Leu Arg Glu Glu 1430 1440

- Pro Ile His Ile Leu Asn Val Ser Ile Gln Cys Ala Asp His Leu 1445 1450 1455
- Glu Asp Glu Ala Leu Val Pro  $\,$  Ile Leu Arg Thr Phe  $\,$  Val Gln Ser  $\,$  1460  $\,$  1465  $\,$  1470
- Lys Lys Asn Ile Leu Val Asp Tyr Gly Leu Arg Arg Ile Pro Phe 1475 1480 1485
- Leu Ile Ala Gln Glu Lys Glu Phe Pro Lys Phe Phe Thr Phe Arg 1490 1495 1500
- Ala Arg Asp Glu Phe Ala Glu Asp Arg Ile Tyr Arg His Leu Glu 1505 1510 1515
- Pro Ala Leu Ala Phe Gln Leu Glu Leu Asn Arg Met Arg Asn Phe 1520 1530
- Asp Leu Thr Ala Val Pro Cys Ala Asn His Lys Met His Leu Tyr 1535 1540 1545
- Leu Gly Ala Ala Lys Val Glu Gly Arg Tyr Glu Val Thr Asp His 1550 1560
- Arg Phe Phe Ile Arg Ala Ile Ile Arg His Ser Asp Leu Ile Thr 1565 1570 1575
- Lys Glu Ala Ser Phe Glu Tyr Leu Gln Asn Glu Gly Glu Arg Leu 1580 1585 1590
- Leu Leu Glu Ala Met Asp Glu Leu Glu Val Ala Phe Asn Asn Thr 1595 1600 1605
- Asn Val Arg Thr Asp Cys Asn His Ile Phe Leu Asn Phe Val Pro 1610 1615 1620
- Thr Val Ile Met Asp Pro Asn Lys Ile Glu Glu Ser Val Arg Tyr 1625 1630 1635
- Met Val Met Arg Tyr Gly Ser Arg Leu Trp Lys Leu Arg Val Leu 1640 1645 1650

- Gln Ala Glu Val Lys Ile Asn Ile Arg Gln Thr Thr Thr Gly Ser 1655 1660 1665
- Ala Val· Pro Ile Arg Leu Phe Ile Thr Asn Glu Ser Gly Tyr Tyr 1670 1680
- Leu Asp Ile Ser Leu Tyr Lys Glu Val Thr Asp Ser Arg Ser Gly 1685 1690 1695
- Asn Ile Met Phe His Ser Phe Gly Asn Lys Gln Gly Pro Gln His 1700 1705 1710
- Gly Met Leu Ile Asn Thr Pro Tyr Val Thr Lys Asp Leu Leu Gln 1715 1720 1725
- Ala Lys Arg Phe Gln Ala Gln Thr Leu Gly Thr Thr Tyr Ile Tyr 1730 1735 1740
- Asp Phe Pro Glu Met Phe Arg Gln Ala Leu Phe Lys Leu Trp Gly 1745 1750 1755
- Ser Pro Asp Lys Tyr Pro Lys Asp Ile Leu Thr Tyr Thr Glu Leu 1760 1765 1770
- Val Leu Asp Ser Gln Gly Gln Leu Val Glu Met Asn Arg Leu Pro 1775 1780 1785
- Gly Gly Asn Glu Val Gly Met Val Ala Phe Lys Met Arg Phe Lys 1790 1795 1800
- Thr Gln Glu Tyr Pro Glu Gly Arg Asp Val Ile Val Ile Gly Asn 1805 1810 1815
- Asp Ile Thr Phe Arg Ile Gly Ser Phe Gly Pro Gly Glu Asp Leu 1820 1825 1830
- Leu Tyr Leu Arg Ala Ser Glu Met Ala Arg Ala Glu Ala Ile Pro 1835 1840 1845
- Lys Ile Tyr Val Ala Ala Asn Ser Gly Ala Arg Ile Gly Met Ala 1850 1855 1860
- Glu Glu Ile Lys His Met Phe His Val Ala Trp Val Asp Pro Glu

1865 1870 1875

| Asp | Pro<br>1880 | His | Lys | Gly | Phe | Lys<br>1885 | Tyr | Leu  | Tyr | Leu | Thr<br>1890  | Pro | Gln | Asp |
|-----|-------------|-----|-----|-----|-----|-------------|-----|------|-----|-----|--------------|-----|-----|-----|
| Tyr | Thr<br>1895 | _   | Ile | Ser | Ser | Leu<br>1900 | Asn | Ser  | Val | His | Cys<br>1905  | Lys | His | Ile |
| Glu | Glu<br>1910 | Gly | Gly | Glu | Ser | Arg<br>1915 |     | Met  | Ile | Thr | Asp<br>1920  | Ile | Ile | Gly |
| Lys | Asp<br>1925 | Asp | Gly | Leu | Gly | Val<br>1930 | Glu | Asn  | Leu | Arg | Gly<br>1935  | Ser | Gly | Met |
| Ile | Ala<br>1940 | Gly | Glu | Ser | Ser | Leu<br>1945 | Ala | Tyr  | Glu | Glu | Ile<br>1950  | Val | Thr | Ile |
| Ser | Leu<br>1955 | Val | Thr | Cys |     | Ala<br>1960 |     | Gly  | Ile |     | Ala<br>,1965 | Tyr | Leu | Val |
| Arg | Leu<br>1970 | Gly | Gln | Arg | Val | Ile<br>1975 |     | Val  | Glu |     | Ser<br>1980  | His | Ile | Ile |
| Leu | Thr<br>1985 | Gly | Ala | Ser | Ala | Leu<br>1990 |     | Lys  | Val | Leu | Gly<br>1995  | Arg | Glu | Val |
| Tyr | Thr<br>2000 | Ser | Asn | Asn | Gln | Leu<br>2005 | Gly | Gly  | Val | Gln | Ile<br>2010  | Met | His | Tyr |
| Asn | Gly<br>2015 | Val | Ser | His | Ile | Thr<br>2020 | Val | Pro  | Asp | Asp | Phe<br>2025  | Glu | Gly | Val |
| Tyr | Thr<br>2030 | Ile | Leu | Glu | Trp | Leu<br>2035 | Ser | Tyr. | Met | Pro | Lys<br>2040  | Asp | Asn | His |
| Ser | Pro<br>2045 | Val | Pro | Ile | Ile | Thr<br>2050 | Pro | Thr  | Asp | Pro | Ile<br>2055  | Asp | Arg | Glu |
| Ile | Glu<br>2060 | Phe | Leu | Pro | Ser | Arg<br>2065 | Ala | Pro  | Tyr | Asp | Pro<br>2070  | Arg | Trp | Met |
| Leu | Ala<br>2075 | Gly | Arg | Pro | His | Pro<br>2080 | Thr | Leu  | Lys | Gly | Thr<br>2085  | Trp | Gln | Ser |

- Gly Phe Phe Asp His Gly Ser Phe Lys Glu Ile Met Ala Pro Trp 2090 2095 2100
- Ala Gln Thr Val Val Thr Gly Arg Ala Arg Leu Gly Gly Ile Pro 2105 2110 2115
- Val Gly Val Ile Ala Val Glu Thr Arg Thr Val Glu Val Ala Val 2120 2125 2130
- Pro Ala Asp Pro Ala Asn Leu Asp Ser Glu Ala Lys Ile Ile Gln 2135 2140 2145
- Gln Ala Gly Gln Val Trp Phe Pro Asp Ser Ala Tyr Lys Thr Ala 2150 2155 2160
- Gln Ala Ile Lys Asp Phe Asn Arg Glu Lys Leu Pro Leu Met Ile 2165 2170 2175
- Phe Ala Asn Trp Arg Gly Phe Ser Gly Gly Met Lys Asp Met Tyr 2180 2185 2190
- Asp Gln Val Leu Lys Phe Gly Ala Tyr Ile Val Asp Gly Leu Arg 2195 2200 2205
- Leu Arg Gly Gly Ser Trp Val Val Ile Asp Ala Thr Ile Asn Pro 2225 2230 2235
- Leu Cys Ile Glu Met Tyr Ala Asp Lys Glu Ser Arg Gly Gly Val 2240 2245 2250
- Leu Glu Pro Glu Gly Thr Val Glu Ile Lys Phe Arg Lys Glu Asp 2255 2260 2265
- Leu Ile Lys Ser Met Arg Arg Ile Asp Pro Ala Tyr Lys Lys Leu 2270 2275 2280
- Met Glu Gln Leu Gly Glu Pro Asp Leu Ser Asp Lys Asp Arg Lys 2285 2290 2295

Asp Leu Glu Gly Arg Leu Lys Ala Arg Glu Asp Leu Leu Pro 2300 2305 2310

Ile Tyr His Gln Val Ala Val Gln Phe Ala Asp Phe His Asp Thr 2315 2320 2325

Pro Gly Arg Met Leu Glu Lys Gly Val Ile Ser Asp Ile Leu Glu 2330 2335 2340

Trp Lys Thr Ala Arg Thr Phe Leu Tyr Trp Arg Leu Arg Arg Leu 2345 2350 2355

Leu Leu Glu Asp Gln Val Lys Gln Glu Ile Leu Gln Ala Ser Gly 2360 2365 2370

Glu Leu Ser His Val His Ile Gln Ser Met Leu Arg Arg Trp Phe 2375 2380 2385

Val Glu Thr Glu Gly Ala Val Lys Ala Tyr Leu Trp Asp Asn Asn 2390 2395 2400

Gln Val Val Gln Trp Leu Glu Gln His Trp Gln Ala Gly Asp 2405 2410 2415

Gly Pro Arg Ser Thr Ile Arg Glu Asn Ile Thr Tyr Leu Lys His 2420 2425 2430

Asp Ser Val Leu Lys Thr Ile Arg Gly Leu Val Glu Glu Asn Pro 2435 2440 2445

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Arg Gln Lys Ile Arg Ser Leu Asp Val Val Gly Lys Ile Lys Arg Glu 50 55 60

Ile Gln Asn Leu Lys Leu Phe Arg His Pro His Ile Ile Lys Leu Tyr 65 70 75 80

Gln Val Ile Ser Thr Pro Thr Asp Phe Phe Met Val Met Glu Tyr Val 85 90 95

Ser Gly Glu Leu Phe Asp Tyr Ile Cys Lys His Gly Arg Val Glu 100 105 110

Glu Met Glu Ala Arg Arg Leu Phe Gln Gln Ile Leu Ser Ala Val Asp 115 120 125

Tyr Cys His Arg His Met Val Val His Arg Asp Leu Lys Pro Glu Asn 130 135 140

Val Leu Leu Asp Ala His Met Asn Ala Lys Ile Ala Asp Phe Gly Leu 145 150 155 160

Ser Asn Met Met Ser Asp Gly Glu Phe Leu Arg Thr Ser Cys Gly Ser 165 170 175

Pro Asn Tyr Ala Ala Pro Glu Val Ile Ser Gly Arg Leu Tyr Ala Gly
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Pro Glu Val Asp.Ile Trp Ser Cys Gly Val Ile Leu Tyr Ala Leu Leu 195 200 205

Cys Gly Thr Leu Pro Phe Asp Asp Glu His Val Pro Thr Leu Phe Lys 210 215 220

| Lys<br>225 | Ile        | Arg        | Gly        | Gly        | Val<br>230 | Phe        | Tyr        | Ile        | Pro        | Glu<br>235 | Tyr        | Leu        | Asn        | Arg        | Ser<br>240 |
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|            | 370        |            |            |            |            | 375        |            |            |            |            | 380        |            |            |            | Leu        |
| 385        |            |            |            |            | 390        |            |            |            |            | 395        |            |            |            |            | Ala<br>400 |
|            |            |            |            | 405        | Ile        |            |            |            | 410        |            |            |            |            | 415        |            |
|            |            | •          | 420        |            |            | •          |            | 425        |            |            |            |            | 430        |            | Val        |
| Val        | Asn        | Ala<br>435 |            | His        | Leu        | Arg        | Val<br>440 | Arg        | Arg        | Lys        | Asn        | Pro<br>445 | Val        | Thr        | Gly        |

Asn Tyr Val Lys Met Ser Leu Gln Leu Tyr Leu Val Asp Asn Arg Ser 455 450 Tyr Leu Leu Asp Phe Lys Ser Ile Asp Asp Glu Val Val Glu Gln Arg 475 470 465 Ser Gly Ser Ser Thr Pro Gln Arg Ser Cys Ser Ala Ala Gly Leu His 490 485 Arg Pro Arg Ser Ser Phe Asp Ser Thr Thr Ala Glu Ser His Ser Leu 500 505 Ser Gly Ser Leu Thr Gly Ser Leu Thr Gly Ser Thr Leu Ser Ser Val 515 520 Ser Pro Arg Leu Gly Ser His Thr Met Asp Phe Phe Glu Met Cys Ala 535 Ser Leu Ile Thr Thr Leu Ala Arg 545 550 <210> 6 <211> 21 <212> DNA <213> Artificial <220> <223> siRNA sense strand oligonucleotide <400> 6 21 cgtgaagaag agctctgggt t <210> 7 <211> 21 <212> DNA <213> Artificial <220> <223> siRNA sense strand oligonucleotide <400> 7 21 gaagatggtg gagaagtgct t <210> 8 <211> 21

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| Ser               | Gly        | Gly               | Ser<br>20  | Gly               | Ser               | Gly        | Gly               | Leu<br>25  | Ile               | Gly               | Leu        | Met               | Lys<br>30  | Asp               | Ala               |     |
|-------------------|------------|-------------------|------------|-------------------|-------------------|------------|-------------------|------------|-------------------|-------------------|------------|-------------------|------------|-------------------|-------------------|-----|
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | ccg<br>Pro        |                   | 144 |
|                   |            |                   |            |                   |                   |            |                   |            |                   | Cys               |            |                   |            | atg<br>Met        |                   | 192 |
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | aat<br>Asn        |                   | 240 |
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | ctc<br>Leu<br>95  |                   | 288 |
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | gaa<br>Glu        |                   | 336 |
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | aag<br>Lys        |                   | 384 |
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | gag<br>Glu        |                   | 432 |
| tct<br>Ser<br>145 | cag<br>Gln | cct<br>Pro        | agg<br>Arg | cga<br>Arg        | aac<br>Asn<br>150 | cta<br>Leu | acc<br>Thr        | aaa<br>Lys | ctg<br>Leu        | tcc<br>Ser<br>155 | ctc<br>Leu | atc<br>Ile        | ttc<br>Phe | agc<br>Ser        | cac<br>His<br>160 | 480 |
| atg<br>Met        | ctg<br>Leu | gca<br>Ala        | gaa<br>Glu | cta<br>Leu<br>165 | aaa<br>Lys        | gga<br>Gly | atc<br>Ile        | ttt<br>Phe | cca<br>Pro<br>170 | agt<br>Ser        | gga<br>Gly | ctc<br>Leu        | ttt<br>Phe | cag<br>Gln<br>175 | gga<br>Gly        | 528 |
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | aga<br>Arg        |                   | 576 |
| gct<br>Ala        | ttt<br>Phe | ggg<br>Gly<br>195 | gaa<br>Glu | aag<br>Lys        | aca<br>Thr        | ata<br>Ile | gtc<br>Val<br>200 | cct<br>Pro | tgg<br>Trp        | aag<br>Lys        | agc<br>Ser | ttt<br>Phe<br>205 | cga<br>Arg | cag<br>Gln        | gct<br>Ala        | 624 |
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | gct<br>Ala        |                   | 672 |
|                   |            |                   |            |                   |                   |            |                   |            |                   |                   |            |                   |            | ttt<br>Phe        |                   | 720 |
| ttt<br>Phe        | gac<br>Asp | atc<br>Ile        | ttt<br>Phe | acc<br>Thr        | cga<br>Arg        | ctc<br>Leu | ttt<br>Phe        | cag<br>Gln | ccc<br>Pro        | tgg<br>Trp        | tcc<br>Ser | tct<br>Ser        | ttg<br>Leu | ctc<br>Leu        | agg<br>Arg        | 768 |

245 250 255

|            |            |                   |            |            | gct<br>Ala        |            |                   |            |            |            |            |                   |            |            |            | 816  |
|------------|------------|-------------------|------------|------------|-------------------|------------|-------------------|------------|------------|------------|------------|-------------------|------------|------------|------------|------|
|            |            |                   |            |            | aaa<br>Lys        |            |                   |            |            |            |            |                   |            |            |            | 864  |
| ggc        |            |                   |            |            | cgg<br>Arg        |            |                   |            |            |            |            |                   |            |            |            | 912  |
|            |            |                   |            |            | gct<br>Ala<br>310 |            |                   |            |            |            |            |                   |            |            |            | 960  |
|            |            |                   |            |            | caa<br>Gln        | _          | _                 |            |            |            |            |                   |            |            |            | 1008 |
|            |            |                   |            |            | gga<br>Gly        |            |                   |            |            |            |            |                   |            |            |            | 1056 |
|            |            |                   |            |            | caa<br>Gln        |            |                   |            |            |            |            |                   |            |            |            | 1104 |
|            |            |                   |            |            | atg<br>Met        |            |                   |            |            |            |            |                   |            |            |            | 1152 |
|            |            |                   |            |            | gat<br>Asp<br>390 |            |                   |            |            |            |            |                   |            |            |            | 1200 |
|            |            | Ser               | Cys        | Leu        | aca<br>Thr        | Ser        | Trp               | Gln        | Glu        | Ser        | Glu        | Gly               | Gln        | Gly        | Cys        | 1248 |
|            |            |                   |            |            | gaa<br>Glu        |            |                   |            |            |            |            |                   |            |            |            | 1296 |
| ccg<br>Pro | ttt<br>Phe | gat<br>Asp<br>435 | cct<br>Pro | aga<br>Arg | ggg<br>Gly        | agt<br>Ser | ggc<br>Gly<br>440 | agc<br>Ser | ctg<br>Leu | ttg<br>Leu | agg<br>Arg | caa<br>Gln<br>445 | gga<br>Gly | gca<br>Ala | gag<br>Glu | 1344 |
|            |            |                   |            |            | aat<br>Asn        |            |                   |            |            |            |            |                   |            |            |            | 1392 |
|            |            |                   |            |            | atg<br>Met<br>470 |            |                   |            |            |            |            |                   |            |            |            | 1440 |

| _          |                   |            |            |            |            |                   |            | cca<br>Pro        |            |            |                   |            |            |            |            | 1488 |  |
|------------|-------------------|------------|------------|------------|------------|-------------------|------------|-------------------|------------|------------|-------------------|------------|------------|------------|------------|------|--|
|            |                   |            |            |            |            |                   |            | cag<br>Gln<br>505 |            |            |                   |            |            |            |            | 1536 |  |
|            |                   |            |            |            |            |                   |            | aag<br>Lys        |            |            |                   |            |            |            |            | 1584 |  |
|            |                   |            |            |            |            |                   |            | ccc<br>Pro        |            |            |                   |            |            |            |            | 1632 |  |
|            |                   |            |            |            |            |                   |            | tct<br>Ser        |            |            |                   |            |            |            |            | 1680 |  |
|            |                   |            |            |            |            |                   |            | cca<br>Pro        |            |            |                   |            |            |            |            | 1728 |  |
|            |                   |            |            |            |            |                   |            | cgc<br>Arg<br>585 |            |            |                   |            |            |            |            | 1776 |  |
|            |                   |            |            |            |            |                   |            | tct<br>Ser        |            |            |                   |            |            |            |            | 1824 |  |
|            |                   |            |            |            |            |                   |            | cgg<br>Arg        |            |            |                   |            |            |            |            | 1872 |  |
|            |                   |            |            |            |            |                   |            | gat<br>Asp        |            |            |                   |            |            |            |            | 1920 |  |
|            |                   |            |            |            |            |                   |            | atg<br>Met        |            |            |                   |            |            |            |            | 1968 |  |
|            |                   |            |            |            |            |                   |            | aaa<br>Lys<br>665 |            |            |                   |            |            |            |            | 2016 |  |
|            |                   |            |            |            |            |                   |            | ctt<br>Leu        |            |            |                   |            |            |            |            | 2064 |  |
| ggg<br>Gly | gag<br>Glu<br>690 | caa<br>Gln | tgt<br>Cys | gag<br>Glu | ggt<br>Gly | gaa<br>Glu<br>695 | gag<br>Glu | gac<br>Asp        | aca<br>Thr | gag<br>Glu | tac<br>Tyr<br>700 | atg<br>Met | act<br>Thr | ccc<br>Pro | tct<br>Ser | 2112 |  |

.

|  |  | cgg<br>Arg        |   | _ | _ |  | _   |  |  |   | 2160 |
|--|--|-------------------|---|---|---|--|-----|--|--|---|------|
|  |  | cag<br>Gln<br>725 |   |   |   |  |     |  |  |   | 2208 |
|  |  | gcg<br>Ala        |   |   |   |  |     |  |  | ٠ | 2256 |
|  |  | gca<br>Ala        |   |   |   |  |     |  |  |   | 2304 |
|  |  | ggg<br>Gly        |   |   |   |  |     |  |  |   | 2352 |
|  |  | act<br>Thr        |   |   |   |  |     |  |  |   | 2400 |
|  |  | ctg<br>Leu<br>805 |   |   |   |  |     |  |  |   | 2448 |
|  |  | gag<br>Glu        |   |   |   |  |     |  |  |   | 2496 |
|  |  | gct<br>Ala        |   |   |   |  |     |  |  |   | 2544 |
|  |  | gcc<br>Ala        |   |   |   |  |     |  |  |   | 2592 |
|  |  | tac<br>Tyr        |   |   |   |  |     |  |  |   | 2640 |
|  |  | atc<br>Ile<br>885 |   |   |   |  |     |  |  |   | 2688 |
|  |  | cct<br>Pro        | _ |   |   |  | tag |  |  |   | 2721 |

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Phe Gln Pro His His His His His His Leu Ser Pro His Pro Pro 35 40 45

Gly Thr Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp 50 60

Lys Val Val Arg Leu Cys Gln Asn Pro Lys Leu Ala Leu Lys Asn Ser 65 70 75 80

Pro Pro Tyr Ile Leu Asp Leu Leu Pro Asp Thr Tyr Gln His Leu Arg 85 90 95

Thr Ile Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn 100 105 110

Glu Tyr Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln 115 120 125

Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn 130 135 140

Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His 145 150 155 160

Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly 165 170 175

Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys 180 185 190

Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala 195 200 205

| Leu        | His<br>210 | Glu        | Val        | His        | Pro        | Ile<br>215 | Ser        | Ser        | Gly        | Leu        | Glu<br>220 | Ala        | Met        | Ala        | Leu        |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Lys<br>225 | Ser        | Thr        | Ile        | Asp        | Leu<br>230 | Thr        | Cys        | Asn        | Asp        | Tyr<br>235 | Ile        | Ser        | Val        | Phe        | Glu<br>240 |
| Phe        | Asp        | Ile        | Phe        | Thr<br>245 | Arg        | Leu        | Phe        | Gln        | Pro<br>250 | Trp        | Ser        | Ser        | Leu        | Leu<br>255 | Arg        |
| Asn        | Trp        | Asn        | Ser<br>260 | Leu        | Ala        | Val        | Thr        | His<br>265 | Pro        | Gly        | Tyr        | Met        | Ala<br>270 | Phe        | Leu        |
| Thr        | Tyr        | Asp<br>275 | Glu        | Val        | Lys        | Ala        | Arg<br>280 | Leu        | Gln        | Lys        | Phe        | Ile<br>285 | His        | Lys        | Pro        |
| Gly        | Ser<br>290 | Tyr        | Ile        | Phe        | Arg        | Leu<br>295 | Ser        | Cys        | Thr        | Arg        | Leu<br>300 | Gly        | Gln        | Trp        | Ala        |
| Ile<br>305 | Glu        | Tyr        | Val        | Thr        | Ala<br>310 | Asp        | Gly        | Asn        | Ile        | Leu<br>315 | Gln        | Thr        | Ile        | Pro        | His<br>320 |
| Asn        | Lys        | Pro        | Leu        | Phe<br>325 | Gln        | Ala        | Leu        | Ile        | Asp<br>330 | Gly        | Phe        | Arg        | Glu        | Gly<br>335 | Phe        |
| Tyr        | Leu        | Phe        | Pro<br>340 | Asp        | Gly        | Arg        | Asn        | Gln<br>345 | Asn        | Pro        | Asp        | Leu        | Thr<br>350 | Gly        | Leu        |
| Cys        | Glu        | Pro<br>355 | Thr        | Pro        | Gln        | Asp        | His<br>360 | Ile        | Lys        | Val        | Thr        | Gln<br>365 | Glu        | Gln        | Tyr        |
| Glu        | Leu<br>370 | Tyr        | Cys        | Glu        | Met        | Gly<br>375 | Ser        | Thr        | Phe        | Gln        | Leu<br>380 | Cys        | Lys        | Ile        | Cys        |
| Ala<br>385 | Glu        | Asn        | Asp        | Lys        | Asp<br>390 | Val        | Lys        | Ile        | Glu        | Pro<br>395 | Cys        | Gly        | His        | Leu        | Met<br>400 |
| Cys        | Thr        | Ser        | Cys        | Leu<br>405 | Thr        | Ser        | Trp        | Gln        | Glu<br>410 | Ser        | Glu        | Gly        | Gln        | Gly<br>415 | Cys        |
| Pro        | Phe        | Cys        | Arg<br>420 | Cys        | Glu        | Ile        | Lys        | Gly<br>425 | Thr        | Glu        | Pro        | Ile        | Val<br>430 | Val        | Asp        |

Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Glu Arg Ala Asp Asp Thr Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg Pro Pro Ser Pro Phe Ser Met Ala Pro Gln Ala Ser Leu Pro Pro Val Pro Pro Arg Leu Asp Leu Leu Pro Gln Arg Val Cys Val Pro Ser Ser Ala Ser Ala Leu Gly Thr Ala Ser Lys Ala Ala Ser Gly Ser Leu His Lys Asp Lys Pro Leu Pro Val Pro Pro Thr Leu Arg Asp Leu Pro Pro Pro Pro Pro Pro Asp Arg Pro Tyr Ser Val Gly Ala Glu Ser Arg Pro Gln Arg Arg Pro Leu Pro Cys Thr Pro Gly Asp Cys Pro Ser Arg Asp Lys Leu Pro Pro Val Pro Ser Ser Arg Leu Gly Asp Ser Trp Leu Pro Arg Pro Ile Pro Lys Val Pro Val Ser Ala Pro Ser Ser Ser Asp Pro Trp Thr Gly Arg Glu Leu Thr Asn Arg His Ser Leu Pro Phe Ser Leu Pro Ser Gln Met Glu Pro Arg Pro Asp Val Pro Arg Leu Gly Ser Thr Phe Ser Leu Asp Thr Ser Met Ser Met Asn Ser Ser Pro Leu Val Gly Pro Glu Cys Asp His Pro Lys Ile Lys Pro Ser Ser Ala Asn Ala

Ile Tyr Ser Leu Ala Ala Arg Pro Leu Pro Val Pro Lys Leu Pro Pro Gly Glu Gln Cys Glu Gly Glu Glu Asp Thr Glu Tyr Met Thr Pro Ser Ser Arg Pro Leu Arg Pro Leu Asp Thr Ser Gln Ser Ser Arg Ala Cys Asp Cys Asp Gln Gln Ile Asp Ser Cys Thr Tyr Glu Ala Met Tyr Asn Ile Gln Ser Gln Ala Pro Ser Ile Thr Glu Ser Ser Thr Phe Gly Glu Gly Asn Leu Ala Ala Ala His Ala Asn Thr Gly Pro Glu Glu Ser Glu Asn Glu Asp Asp Gly Tyr Asp Val Pro Lys Pro Pro Val Pro Ala Val Leu Ala Arg Arg Thr Leu Ser Asp Ile Ser Asn Ala Ser Ser Ser Phe Gly Trp Leu Ser Leu Asp Gly Asp Pro Thr Thr Asn Val Thr Glu Gly Ser Gln Val Pro Glu Arg Pro Pro Lys Pro Phe Pro Arg Arg Ile Asn Ser Glu Arg Lys Ala Gly Ser Cys Gln Gln Gly Ser Gly Pro Ala Ala Ser Ala Ala Thr Ala Ser Pro Gln Leu Ser Ser Glu Ile Glu Asn Leu Met Ser Gln Gly Tyr Ser Tyr Gln Asp Ile Gln Lys Ala Leu Val Ile

Ala Gln Asn Asn Ile Glu Met Ala Lys Asn Ile Leu Arg Glu Phe Val

## Ser Ile Ser Ser Pro Ala His Val Ala Thr 900 905

| <210<br><211<br><212<br><213 | > :<br>> :        | 251<br>2721<br>DNA<br>Artif | icia             | ıl               | ,                |                   |                   |                  |                  | ٠                |                   |                   |                  |                  |                  |     |
|------------------------------|-------------------|-----------------------------|------------------|------------------|------------------|-------------------|-------------------|------------------|------------------|------------------|-------------------|-------------------|------------------|------------------|------------------|-----|
| <220<br><223                 |                   | c-Cbl                       | . C38            | 31A              |                  |                   |                   |                  |                  |                  |                   |                   |                  |                  |                  |     |
| <220<br><221<br><222         | >                 | CDS<br>(1)                  | . (271           | L8)              |                  |                   |                   |                  |                  |                  |                   |                   | •                |                  |                  |     |
| <400<br>atg<br>Met<br>1      | gcc               | 251<br>.ggc<br>Gly          | aac<br>Asn       | gtg<br>Val<br>5  | aag<br>Lys       | aag<br>Lys        | agc<br>Ser        | tct<br>Ser       | ggg<br>Gly<br>10 | gcc<br>Ala       | gly<br>ggg        | ggc<br>Gly        | ggc<br>Gly       | acg<br>Thr<br>15 | ggc<br>Gly       | 48  |
| tcc<br>Ser                   | ggg<br>Gly        | ggc<br>Gly                  | tcg<br>Ser<br>20 | ggt<br>Gly       | tcg<br>Ser       | ggt<br>Gly        | ggc<br>Gly        | ctg<br>Leu<br>25 | att<br>Ile       | ggg<br>Gly       | ctc<br>Leu        | atg<br>Met        | aag<br>Lys<br>30 | gac<br>Asp       | gcc<br>Ala       | 96  |
| ttc<br>Phe                   | cag<br>Gln        | ccg<br>Pro<br>35            | cac<br>His       | cac<br>His       | cac<br>His       | cac<br>His        | cac<br>His<br>40  | cac<br>His       | cac<br>His       | ctc<br>Leu       | agc<br>Ser        | ccc<br>Pro<br>45  | cac<br>His       | ccg<br>Pro       | ccg<br>Pro       | 144 |
| ggg                          | acg<br>Thr<br>50  | gtg<br>Val                  | gac<br>Asp       | aag<br>Lys       | aag<br>Lys       | atg<br>Met<br>55  | gtg<br>Val        | gag<br>Glu       | aag<br>Lys       | tgc<br>Cys       | tgg<br>Trp<br>60  | aag<br>Lys        | ctc<br>Leu       | atg<br>Met       | gac<br>Asp       | 192 |
| aag<br>Lys<br>65             | gtg<br>Val        | gtg<br>Val                  | cgg<br>Arg       | ttg<br>Leu       | tgt<br>Cys<br>70 | cag<br>Gln        | aac<br>Asn        | cca<br>Pro       | aag<br>Lys       | ctg<br>Leu<br>75 | gcg<br>Ala        | cta<br>Leu        | aag<br>Lys       | aat<br>Asn       | agc<br>Ser<br>80 | 240 |
| cca<br>Pro                   | cct<br>Pro        | tat<br>Tyr                  | atc<br>Ile       | tta<br>Leu<br>85 | gac<br>Asp       | ctg<br>Leu        | cta<br>Leu        | cca<br>Pro       | gat<br>Asp<br>90 | acc<br>Thr       | tac<br>Tyr        | cag<br>Gln        | cat<br>His       | ctc<br>Leu<br>95 | cgt<br>Arg       | 288 |
|                              |                   | ttg<br>Leu                  |                  |                  |                  |                   |                   |                  |                  |                  |                   |                   |                  |                  |                  | 336 |
| gag<br>Glu                   | tat<br>Tyr        | ttt<br>Phe<br>115           | agg<br>Arg       | gtg<br>Val       | ttt<br>Phe       | atg<br>Met        | gag<br>Glu<br>120 | aat<br>Asn       | ttg<br>Leu       | atg<br>Met       | aag<br>Lys        | aaa<br>Lys<br>125 | act<br>Thr       | aag<br>Lys       | caa<br>Gln       | 384 |
| acc<br>Thr                   | ata<br>Ile<br>130 | agc<br>Ser                  | ctc<br>Leu       | ttc<br>Phe       | aag<br>Lys       | gag<br>Glu<br>135 | gga<br>Gly        | aaa<br>Lys       | gaa<br>Glu       | aga<br>Arg       | atg<br>Met<br>140 | tat<br>Tyr        | gag<br>Glu       | gag<br>Glu       | aat<br>Asn       | 432 |
| tct                          | cag               | cct                         | agg              | cga              | aac              | cta               | acc               | aaa              | ctg              | tcc              | ctc               | atc               | ttc              | agc              | cac              | 480 |

|   | Ser<br>145 | Gln        | Pro               | Arg        | Arg               | Asn<br>150 | Leu        | Thr               | Lys        | Leu        | Ser<br>155 | Leu        | Ile               | Phe        | Ser        | His<br>160 |     | ,  |  |  |
|---|------------|------------|-------------------|------------|-------------------|------------|------------|-------------------|------------|------------|------------|------------|-------------------|------------|------------|------------|-----|----|--|--|
|   |            |            |                   |            | cta<br>Leu<br>165 |            |            |                   |            |            |            |            |                   |            |            |            | 52  | 8  |  |  |
|   |            |            |                   |            | att<br>Ile        |            |            |                   |            |            |            |            |                   |            |            |            | 57  | 6  |  |  |
| · |            |            |                   |            | aag<br>Lys        |            |            |                   |            |            |            |            |                   |            |            |            | 62  | 4  |  |  |
|   |            |            |                   |            | cat<br>His        |            |            |                   |            |            |            |            |                   |            |            |            | 67  | 2  |  |  |
|   |            |            |                   |            | gat<br>Asp        |            |            |                   |            |            |            |            |                   |            |            |            | 72  | 0  |  |  |
|   |            |            |                   |            | acc<br>Thr<br>245 |            |            |                   |            |            |            |            |                   |            |            |            | 76  | 8  |  |  |
|   |            |            |                   |            | ctt<br>Leu        |            |            |                   |            |            |            |            |                   |            |            |            | 81  | 6  |  |  |
|   | acg<br>Thr | tat<br>Tyr | gac<br>Asp<br>275 | gaa<br>Glu | gtg<br>Val        | aaa<br>Lys | gct<br>Ala | cgg<br>Arg<br>280 | ctc<br>Leu | cag<br>Gln | aaa<br>Lys | ttc<br>Phe | att<br>Ile<br>285 | cac<br>His | aaa<br>Lys | cct<br>Pro | 86  | 4  |  |  |
| · |            |            |                   |            | ttc<br>Phe        |            |            |                   |            |            |            |            |                   |            |            |            | 91  | .2 |  |  |
|   |            |            |                   |            | act<br>Thr        |            |            |                   |            |            |            |            |                   |            |            |            | 96  | 0  |  |  |
|   |            |            |                   |            | ttc<br>Phe<br>325 |            |            |                   |            |            |            |            |                   |            |            |            | 100 | 8  |  |  |
|   |            |            |                   |            | gat<br>Asp        |            |            |                   |            |            |            |            |                   |            |            |            | 105 | 66 |  |  |
|   |            |            |                   |            | ccc<br>Pro        |            |            |                   |            |            |            |            |                   |            |            |            | 110 | 14 |  |  |
|   |            |            |                   |            | gag<br>Glu        |            |            |                   |            |            |            |            |                   |            |            |            | 115 | 52 |  |  |

370 375 380

|  |  |  | aag<br>Lys        |  |  |  |  | 1: | 200      |
|--|--|--|-------------------|--|--|--|--|----|----------|
|  |  |  | tgg<br>Trp        |  |  |  |  | 1  | 248      |
|  |  |  | aaa<br>Lys        |  |  |  |  | 1: | 296      |
|  |  |  | ggc<br>Gly<br>440 |  |  |  |  | 1  | 344      |
|  |  |  | gat<br>Asp        |  |  |  |  | 1  | 392      |
|  |  |  | gaa<br>Glu        |  |  |  |  | 1  | 440      |
|  |  |  | gcc<br>Ala        |  |  |  |  | 1  | 488      |
|  |  |  | ccg<br>Pro        |  |  |  |  | 1  | 536      |
|  |  |  | tct<br>Ser<br>520 |  |  |  |  | 1  | 584      |
|  |  |  | cct<br>Pro        |  |  |  |  | 1  | 632      |
|  |  |  | tat<br>Tyr        |  |  |  |  | 1  | 680      |
|  |  |  | aca<br>Thr        |  |  |  |  | 1  | 728      |
|  |  |  | agc<br>Ser        |  |  |  |  |    | 776<br>, |
|  |  |  | gta<br>Val<br>600 |  |  |  |  | 1  | 824      |

|  |  |  |   |   |  |  | ttt<br>Phe        |  | 1872 |
|--|--|--|---|---|--|--|-------------------|--|------|
|  |  |  |   |   |  |  | gga<br>Gly        |  | 1920 |
|  |  |  |   |   |  |  | tta<br>Leu        |  | 1968 |
|  |  |  |   |   |  |  | gcc<br>Ala<br>670 |  | 2016 |
|  |  |  |   |   |  |  | ctg<br>Leu        |  | 2064 |
|  |  |  |   |   |  |  | act<br>Thr        |  | 2112 |
|  |  |  | _ | - |  |  | cga<br>Arg        |  | 2160 |
|  |  |  |   |   |  |  | atg<br>Met        |  | 2208 |
|  |  |  |   |   |  |  | ttt<br>Phe<br>750 |  | 2256 |
|  |  |  |   |   |  |  | gag<br>Glu        |  | 2304 |
|  |  |  |   |   |  |  | ccg<br>Pro        |  | 2352 |
|  |  |  |   |   |  |  | tcc<br>Ser        |  | 2400 |
|  |  |  |   |   |  |  | act<br>Thr        |  | 2448 |
|  |  |  |   |   |  |  | aga<br>Arg<br>830 |  | 2496 |

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|  |                          |                         |                         |                        |                                |                         |                         |                         |                         |                                |                         |                         | cct<br>Pro              |                         |                                | 2544 |
|--|--------------------------|-------------------------|-------------------------|------------------------|--------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------------|------|
|  |                          |                         |                         |                        |                                |                         |                         |                         |                         |                                |                         |                         | gag<br>Glu              |                         |                                | 2592 |
|  |                          |                         |                         |                        |                                |                         |                         |                         |                         |                                |                         |                         | ttg<br>Leu              |                         |                                | 2640 |
|  |                          |                         |                         |                        |                                |                         |                         |                         |                         |                                |                         |                         | gaa<br>Glu              |                         |                                | 2688 |
|  | att<br>Ile               |                         |                         |                        | -                              |                         | -                       |                         |                         | tag                            |                         |                         |                         |                         |                                | 2721 |
| <210<br><211<br><212<br><213               | L> 9<br>2> I             |                         | ficia                   | al                     |                                |                         |                         |                         |                         |                                |                         |                         |                         |                         |                                |      |
| <220<br><223                               |                          | Syntl                   | netio                   | c Cor                  | nstri                          | ıct                     |                         |                         |                         |                                |                         |                         |                         |                         |                                |      |
|  |                          |                         |                         |                        |                                |                         |                         |                         |                         |                                |                         |                         |                         |                         |                                |      |
| <400                                       | )> 2                     | 252                     |                         |                        |                                |                         |                         |                         |                         |                                |                         |                         |                         |                         |                                |      |
|  |                          |                         | Asn                     | Val<br>5               | Lys                            | Lys                     | Ser                     | Ser                     | Gly<br>10               | Ala                            | Gly                     | Gly                     | Gly                     | Thr<br>15               | Gly                            |      |
| Met<br>1                                   | Ala                      | Gly                     |                         | 5                      | _                              |                         |                         |                         | 10                      |                                |                         |                         | Gly<br>Lys<br>30        | 15                      |                                |      |
| Met<br>1<br>Ser                            | Ala<br>Gly               | Gly<br>Gly              | Ser<br>20               | 5<br>Gly               | Ser                            | Gly                     | Gly                     | Leu<br>25               | 10                      | Gly                            | Leu                     | Met                     | Lys                     | 15<br>Asp               | Ala                            |      |
| Met<br>1<br>Ser<br>Phe                     | Ala<br>Gly<br>Gln        | Gly<br>Gly<br>Pro<br>35 | Ser<br>20<br>His        | 5<br>Gly<br>His        | Ser                            | Gly                     | Gly<br>His<br>40        | Leu<br>25<br>His        | 10<br>Ile<br>His        | Gly<br>Leu                     | Leu                     | Met<br>Pro<br>45        | Lys<br>30               | 15<br>Asp<br>Pro        | Ala<br>Pro                     |      |
| Met<br>1<br>Ser<br>Phe<br>Gly              | Ala<br>Gly<br>Gln<br>Thr | Gly Gly Pro 35          | Ser<br>20<br>His        | 5<br>Gly<br>His<br>Lys | Ser<br>His                     | Gly<br>His<br>Met<br>55 | Gly<br>His<br>40<br>Val | Leu<br>25<br>His<br>Glu | 10<br>Ile<br>His<br>Lys | Gly<br>Leu<br>Cys              | Leu<br>Ser<br>Trp       | Met<br>Pro<br>45<br>Lys | Lys<br>30<br>His        | 15<br>Asp<br>Pro<br>Met | Ala<br>Pro<br>Asp              |      |
| Met<br>1<br>Ser<br>Phe<br>Gly<br>Lys<br>65 | Ala Gly Gln Thr 50 Val   | Gly Pro 35 Val          | Ser<br>20<br>His<br>Asp | Gly<br>His<br>Lys      | Ser<br>His<br>Lys<br>Cys<br>70 | Gly<br>His<br>Met<br>55 | Gly<br>His<br>40<br>Val | Leu<br>25<br>His<br>Glu | 10<br>Ile<br>His<br>Lys | Gly<br>Leu<br>Cys<br>Leu<br>75 | Leu<br>Ser<br>Trp<br>60 | Met Pro 45 Lys          | Lys<br>30<br>His<br>Leu | Asp<br>Pro<br>Met       | Ala<br>Pro<br>Asp<br>Ser<br>80 |      |

Glu Tyr Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala Leu His Glu Val His Pro Ile Ser Ser Gly Leu Glu Ala Met Ala Leu Lys Ser Thr Ile Asp Leu Thr Cys Asn Asp Tyr Ile Ser Val Phe Glu Phe Asp Ile Phe Thr Arg Leu Phe Gln Pro Trp Ser Ser Leu Leu Arg Asn Trp Asn Ser Leu Ala Val Thr His Pro Gly Tyr Met Ala Phe Leu Thr Tyr Asp Glu Val Lys Ala Arg Leu Gln Lys Phe Ile His Lys Pro Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe 

Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Glu Gln Tyr Glu Leu Tyr Cys Glu Met Gly Ser Thr Phe Gln Leu Ala Lys Ile Cys Ala Glu Asn Asp Lys Asp Val Lys Ile Glu Pro Cys Gly His Leu Met Cys Thr Ser Cys Leu Thr Ser Trp Gln Glu Ser Glu Gly Gln Gly Cys Pro Phe Cys Arg Cys Glu Ile Lys Gly Thr Glu Pro Ile Val Val Asp Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Glu Arg Ala Asp Asp Thr Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg Pro Pro Ser Pro Phe Ser Met Ala Pro Gln Ala Ser Leu Pro Pro Val Pro Pro Arg Leu Asp Leu Leu Pro Gln Arg Val Cys Val Pro Ser Ser Ala Ser Ala Leu Gly Thr Ala Ser Lys Ala Ala Ser Gly Ser Leu His Lys Asp Lys Pro Leu Pro Val Pro Pro Thr Leu Arg Asp Leu Pro Pro Pro Pro Pro Pro Asp Arg Pro Tyr Ser Val Gly Ala Glu Ser Arg Pro 

Gln Arg Arg Pro Leu Pro Cys Thr Pro Gly Asp Cys Pro Ser Arg Asp Lys Leu Pro Pro Val Pro Ser Ser Arg Leu Gly Asp Ser Trp Leu Pro Arg Pro Ile Pro Lys Val Pro Val Ser Ala Pro Ser Ser Ser Asp Pro Trp Thr Gly Arg Glu Leu Thr Asn Arg His Ser Leu Pro Phe Ser Leu Pro Ser Gln Met Glu Pro Arg Pro Asp Val Pro Arg Leu Gly Ser Thr Phe Ser Leu Asp Thr Ser Met Ser Met Asn Ser Ser Pro Leu Val Gly Pro Glu Cys Asp His Pro Lys Ile Lys Pro Ser Ser Ser Ala Asn Ala Ile Tyr Ser Leu Ala Ala Arg Pro Leu Pro Val Pro Lys Leu Pro Pro Gly Glu Gln Cys Glu Gly Glu Glu Asp Thr Glu Tyr Met Thr Pro Ser Ser Arg Pro Leu Arg Pro Leu Asp Thr Ser Gln Ser Ser Arg Ala Cys Asp Cys Asp Gln Gln Ile Asp Ser Cys Thr Tyr Glu Ala Met Tyr Asn Ile Gln Ser Gln Ala Pro Ser Ile Thr Glu Ser Ser Thr Phe Gly Glu Gly Asn Leu Ala Ala Ala His Ala Asn Thr Gly Pro Glu Glu Ser Glu Asn Glu Asp Asp Gly Tyr Asp Val Pro Lys Pro Pro Val Pro Ala Val 775 · 

Leu Ala Arg Arg Thr Leu Ser Asp Ile Ser Asn Ala Ser Ser Phe

| 785 | 790 | 795 | 800 |
|-----|-----|-----|-----|
|     |     |     |     |

Gly Trp Leu Ser Leu Asp Gly Asp Pro Thr Thr Asn Val Thr Glu Gly 805 810 815

Ser Gln Val Pro Glu Arg Pro Pro Lys Pro Phe Pro Arg Arg Ile Asn 820 825 830

Ser Glu Arg Lys Ala Gly Ser Cys Gln Gln Gly Ser Gly Pro Ala Ala 835 840 845

Ser Ala Ala Thr Ala Ser Pro Gln Leu Ser Ser Glu Ile Glu Asn Leu 850 855 860

Met Ser Gln Gly Tyr Ser Tyr Gln Asp Ile Gln Lys Ala Leu Val Ile 865 870 875 880

Ala Gln Asn Asn Ile Glu Met Ala Lys Asn Ile Leu Arg Glu Phe Val 885 890 895

Ser Ile Ser Ser Pro Ala His Val Ala Thr 900 905

<210> 253

<211> 2721

<212> DNA

<213> Artificial

<220>

<223> c-Cbl Y700F

<220>

<221> CDS

<222> (1)..(2718)

<400> 253

atg gcc ggc aac gtg aag aag agc tct ggg gcc ggg ggc ggc acg ggc
Met Ala Gly Asn Val Lys Lys Ser Ser Gly Ala Gly Gly Thr Gly
1 5 10 15

48

96

tcc ggg ggc tcg ggt tcg ggt ggc ctg att ggg ctc atg aag gac gcc Ser Gly Gly Ser Gly Ser Gly Gly Leu Ile Gly Leu Met Lys Asp Ala 20 25 30

ttc cag ccg cac cac cac cac cac cac ctc agc ccc cac ccg ccg
Phe Gln Pro His His His His His His Leu Ser Pro His Pro Pro
35 40 45

|            | acg<br>Thr<br>50  |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 192 |   |  |
|------------|-------------------|-------------------|-------------------|------------|------------|-------------------|-------------------|-------------------|------------|------------|-------------------|-------------------|-------------------|------------|------------|-----|---|--|
|            | gtg<br>Val        |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 240 |   |  |
|            | cct<br>Pro        |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 288 | , |  |
| act<br>Thr | atc<br>Ile        | ttg<br>Leu        | tca<br>Ser<br>100 | aga<br>Arg | tat<br>Tyr | gag<br>Glu        | Gly<br>ggg        | aag<br>Lys<br>105 | atg<br>Met | gag<br>Glu | aca<br>Thr        | ctt<br>Leu        | gga<br>Gly<br>110 | gaa<br>Glu | aat<br>Asn | 336 |   |  |
| gag<br>Glu | tat<br>Tyr        | ttt<br>Phe<br>115 | agg<br>Arg        | gtg<br>Val | ttt<br>Phe | atg<br>Met        | gag<br>Glu<br>120 | aat<br>Asn        | ttg<br>Leu | atg<br>Met | aag<br>Lys        | aaa<br>Lys<br>125 | act<br>Thr        | aag<br>Lys | caa<br>Gln | 384 |   |  |
|            | ata<br>Ile<br>130 |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 432 |   |  |
|            | cag<br>Gln        |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 480 |   |  |
|            | ctg<br>Leu        |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 528 |   |  |
|            | aca<br>Thr        |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 576 |   |  |
| gct<br>Ala | ttt<br>Phe        | ggg<br>Gly<br>195 | gaa<br>Glu        | aag<br>Lys | aca<br>Thr | ata<br>Ile        | gtc<br>Val<br>200 | cct<br>Pro        | tgg<br>Trp | aag<br>Lys | agc<br>Ser        | ttt<br>Phe<br>205 | cga<br>Arg        | cag<br>Gln | gct<br>Ala | 624 |   |  |
| cta<br>Leu | cat<br>His<br>210 | gaa<br>Glu        | gtg<br>Val        | cat<br>His | ccc<br>Pro | atc<br>Ile<br>215 | agt<br>Ser        | tct<br>Ser        | ggg        | ctg<br>Leu | gag<br>Glu<br>220 | gcc<br>Ala        | atg<br>Met        | gct<br>Ala | ctg<br>Leu | 672 |   |  |
|            | tcc<br>Ser        |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 720 |   |  |
|            | gac<br>Asp        |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   |            |            | 768 |   |  |
| aat<br>Asn | tgg<br>Trp        | aac<br>Asn        | agc<br>Ser<br>260 | ctt<br>Leu | gct<br>Ala | gta<br>Val        | act<br>Thr        | cat<br>His<br>265 | cct<br>Pro | ggc<br>Gly | tac<br>Tyr        | atg<br>Met        | gct<br>Ala<br>270 | ttt<br>Phe | ttg<br>Leu | 816 |   |  |
| acg        | tat               | gac               | gaa               | gtg        | aaa        | gct               | cgg               | ctc               | cag        | aaa        | ttc               | att               | cac               | aaa        | cct        | 864 |   |  |

| Thr        | Tyr        | Asp<br>275 | Glu        | Val               | Lys        | Ala        | Arg<br>280 | Leu        | Gln               | Lys        | Phe        | Ile<br>285 | His        | Lys               | Pro        |      |
|------------|------------|------------|------------|-------------------|------------|------------|------------|------------|-------------------|------------|------------|------------|------------|-------------------|------------|------|
|            |            |            |            |                   |            |            |            |            | act<br>Thr        |            |            |            |            |                   |            | 912  |
|            |            |            |            |                   |            |            |            |            | att<br>Ile        |            |            |            |            |                   |            | 960  |
|            |            |            |            |                   |            | _          | _          |            | gat<br>Asp<br>330 |            |            |            |            | _                 |            | 1008 |
|            |            |            |            |                   |            |            |            |            | aat<br>Asn        |            |            |            |            |                   |            | 1056 |
|            |            |            |            |                   |            |            |            |            | aaa<br>Lys        |            |            |            |            |                   |            | 1104 |
|            |            |            |            |                   |            |            |            |            | ttc<br>Phe        |            |            |            |            |                   |            | 1152 |
|            |            |            |            |                   |            |            |            |            | gag<br>Glu        |            |            |            |            |                   |            | 1200 |
|            |            |            |            |                   |            |            |            |            | gaa<br>Glu<br>410 |            |            |            |            |                   |            | 1248 |
|            |            |            |            |                   |            |            |            |            | act<br>Thr        |            |            |            |            |                   |            | 1296 |
|            |            |            |            |                   |            |            |            |            | ctg<br>Leu        |            |            |            |            |                   |            | 1344 |
|            |            |            |            |                   |            |            |            |            | gat<br>Asp        |            |            |            |            |                   |            | 1392 |
|            |            |            |            |                   |            |            |            |            | gct<br>Ala        |            |            |            |            |                   |            | 1440 |
| ccg<br>Pro | cct<br>Pro | tct<br>Ser | cca<br>Pro | ttc<br>Phe<br>485 | tcc<br>Ser | atg<br>Met | gcc<br>Ala | cca<br>Pro | caa<br>Gln<br>490 | gct<br>Ala | tcc<br>Ser | ctt<br>Leu | ccc<br>Pro | ccg<br>Pro<br>495 | gtg<br>Val | 1488 |
|            |            |            |            |                   |            |            |            |            | cga<br>Arg        |            |            |            |            |                   |            | 1536 |

500 505 510

|   |  |   | gct<br>Ala        |   |   |  |  |  | 1 | L584      |
|---|--|---|-------------------|---|---|--|--|--|---|-----------|
|   |  |   | gta<br>Val<br>535 |   |   |  |  |  | 1 | L632      |
|   |  |   | cca<br>Pro        |   |   |  |  |  | 1 | L680      |
|   |  |   | tgt<br>Cys        |   |   |  |  |  | 1 | 1728      |
| _ |  | _ | tct<br>Ser        | - | _ |  |  |  | 1 | L776      |
|   |  |   | cca<br>Pro        |   |   |  |  |  | 1 | 1824      |
|   |  |   | acc<br>Thr<br>615 |   |   |  |  |  | 1 | L872<br>· |
|   |  |   | aga<br>Arg        |   |   |  |  |  | 1 | 1920      |
|   |  |   | atg<br>Met        |   |   |  |  |  | 1 | 1968      |
|   |  |   | aaa<br>Lys        |   |   |  |  |  | 2 | 2016      |
|   |  |   | aga<br>Arg        |   |   |  |  |  | 2 | 2064      |
|   |  |   | gaa<br>Glu<br>695 |   |   |  |  |  | 2 | 2112      |
|   |  |   | ttg<br>Leu        |   |   |  |  |  | 2 | 2160      |
|   |  |   | gat<br>Asp        |   |   |  |  |  | 2 | 2208      |

|                          |                   |                           | cag<br>Gln<br>740 |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   | 2256 |
|--------------------------|-------------------|---------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|
|                          |                   |                           | gcc<br>Ala        |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   | 2304 |
| aat<br>Asn               | gag<br>Glu<br>770 | gat<br>Asp                | gat<br>Asp        | Gly<br>ggg        | tat<br>Tyr        | gat<br>Asp<br>775 | gtc<br>Val        | cca<br>Pro        | aag<br>Lys        | cca<br>Pro        | cct<br>Pro<br>780 | gtg<br>Val        | ccg<br>Pro        | gcc<br>Ala        | gtg<br>Val        | 2352 |
| ctg<br>Leu<br>785        | gcc<br>Ala        | cgc<br>Arg                | cga<br>Arg        | act<br>Thr        | ctc<br>Leu<br>790 | tca<br>Ser        | gat<br>Asp        | atc<br>Ile        | tct<br>Ser        | aat<br>Asn<br>795 | gcc<br>Ala        | agc<br>Ser        | tcc<br>Ser        | tcc<br>Ser        | ttt<br>Phe<br>800 | 2400 |
| ggc<br>Gly               | tgg<br>Trp        | ttg<br>Leu                | tct<br>Ser        | ctg<br>Leu<br>805 | gat<br>Asp        | ggt<br>Gly        | gat<br>Asp        | cct<br>Pro        | aca<br>Thr<br>810 | aca<br>Thr        | aat<br>Asn        | gtc<br>Val        | act<br>Thr        | gaa<br>Glu<br>815 | ggt<br>Gly        | 2448 |
| tcc<br>Ser               | caa<br>Gln        | gtt<br>Val                | ccc<br>Pro<br>820 | gag<br>Glu        | agg<br>Arg        | cct<br>Pro        | cca<br>Pro        | aaa<br>Lys<br>825 | cca<br>Pro        | ttc<br>Phe        | ccg<br>Pro        | cgg<br>Arg        | aga<br>Arg<br>830 | atc<br>Ile        | aac<br>Asn        | 2496 |
| tct<br>Ser               | gaa<br>Glu        | cgg<br>Arg<br>835         | aaa<br>Lys        | gct<br>Ala        | ggc<br>Gly        | agc<br>Ser        | tgt<br>Cys<br>840 | cag<br>Gln        | caa<br>Gln        | ggt<br>Gly        | agt<br>Ser        | ggt<br>Gly<br>845 | cct<br>Pro        | gcc<br>Ala        | gcc<br>Ala        | 2544 |
| tct<br>Ser               | gct<br>Ala<br>850 | gcc<br>Ala                | acc<br>Thr        | gcc<br>Ala        | tca<br>Ser        | cct<br>Pro<br>855 | cag<br>Gln        | ctc<br>Leu        | tcc<br>Ser        | agt<br>Ser        | gag<br>Glu<br>860 | atc<br>Ile        | gag<br>Glu        | aac<br>Asn        | ctc<br>Leu        | 2592 |
| atg<br>Met<br>865        | Ser               | cag<br>Gln                | ggg<br>Gly        | tac<br>Tyr        | tcc<br>Ser<br>870 | tac<br>Tyr        | cag<br>Gln        | gac<br>Asp        | atc<br>Ile        | cag<br>Gln<br>875 | aaa<br>Lys        | gct<br>Ala        | ttg<br>Leu        | gtc<br>Val        | att<br>Ile<br>880 | 2640 |
| gcc<br>Ala               | cag<br>Gln        | aac<br>Asn                | aac<br>Asn        | atc<br>Ile<br>885 | Glu               | atg<br>Met        | gcc<br>Ala        | aaa<br>Lys        | aac<br>Asn<br>890 | atc<br>Ile        | ctc<br>Leu        | cgg<br>Arg        | gaa<br>Glu        | ttt<br>Phe<br>895 | gtt<br>Val        | 2688 |
|                          |                   |                           | tct<br>Ser<br>900 |                   |                   |                   |                   |                   |                   | tag               |                   |                   |                   |                   |                   | 2721 |
| <21<br><21<br><21<br><21 | 1><br>2>          | 254<br>906<br>PRT<br>Arti | ficí              | al                |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |      |
| <22<br><22               |                   | Synt                      | heti              | c Co              | nstr              | uct               |                   |                   |                   |                   |                   |                   |                   |                   |                   |      |
|                          |                   |                           |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |      |

Met Ala Gly Asn Val Lys Lys Ser Ser Gly Ala Gly Gly Thr Gly

<400> 254

Ser Gly Gly Ser Gly Ser Gly Leu Ile Gly Leu Met Lys Asp Ala 20 25 30

Phe Gln Pro His His His His His His Leu Ser Pro His Pro Pro 35 40 45

Gly Thr Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp 50 55 60

Lys Val Val Arg Leu Cys Gln Asn Pro Lys Leu Ala Leu Lys Asn Ser 65 70 75 80

Pro Pro Tyr Ile Leu Asp Leu Leu Pro Asp Thr Tyr Gln His Leu Arg 85 90 95

Thr Ile Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn 100 105 110

Glu Tyr Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln
115 120 125

Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn . 130  $\,$  135  $\,$  140

Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His 145 150 155 160

Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly 165 170 175

Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys 180 185 190

Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala 195 200 205

Leu His Glu Val His Pro Ile Ser Ser Gly Leu Glu Ala Met Ala Leu 210 215 220

Lys Ser Thr Ile Asp Leu Thr Cys Asn Asp Tyr Ile Ser Val Phe Glu 225 230 235 240

Phe Asp Ile Phe Thr Arg Leu Phe Gln Pro Trp Ser Ser Leu Leu Arg 245 250 255

Asn Trp Asn Ser Leu Ala Val Thr His Pro Gly Tyr Met Ala Phe Leu 260 265 270

Thr Tyr Asp Glu Val Lys Ala Arg Leu Gln Lys Phe Ile His Lys Pro 275 280 285

Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala 290 295 300

Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His 305 310 315 320

Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe 325 330 335

Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu 340 345 350

Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Glu Gln Tyr 355 360 365

Glu Leu Tyr Cys Glu Met Gly Ser Thr Phe Gln Leu Cys Lys Ile Cys 370 375 380

Ala Glu Asn Asp Lys Asp Val Lys Ile Glu Pro Cys Gly His Leu Met 385 390 395 400

Cys Thr Ser Cys Leu Thr Ser Trp Gln Glu Ser Glu Gly Gln Gly Cys 405 410 415

Pro Phe Cys Arg Cys Glu Ile Lys Gly Thr Glu Pro Ile Val Val Asp 420 425 430

Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu 435 440 445

Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Glu Arg Ala Asp 450 455 460

Asp Thr Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg . Pro Pro Ser Pro Phe Ser Met Ala Pro Gln Ala Ser Leu Pro Pro Val Pro Pro Arg Leu Asp Leu Leu Pro Gln Arg Val Cys Val Pro Ser Ser Ala Ser Ala Leu Gly Thr Ala Ser Lys Ala Ala Ser Gly Ser Leu His Lys Asp Lys Pro Leu Pro Val Pro Pro Thr Leu Arg Asp Leu Pro Pro Pro Pro Pro Pro Asp Arg Pro Tyr Ser Val Gly Ala Glu Ser Arg Pro Gln Arg Arg Pro Leu Pro Cys Thr Pro Gly Asp Cys Pro Ser Arg Asp Lys Leu Pro Pro Val Pro Ser Ser Arg Leu Gly Asp Ser Trp Leu Pro Arg Pro Ile Pro Lys Val Pro Val Ser Ala Pro Ser Ser Ser Asp Pro Trp Thr Gly Arg Glu Leu Thr Asn Arg His Ser Leu Pro Phe Ser Leu Pro Ser Gln Met Glu Pro Arg Pro Asp Val Pro Arg Leu Gly Ser Thr Phe Ser Leu Asp Thr Ser Met Ser Met Asn Ser Ser Pro Leu Val Gly Pro Glu Cys Asp His Pro Lys Ile Lys Pro Ser Ser Ser Ala Asn Ala Ile Tyr Ser Leu Ala Ala Arg Pro Leu Pro Val Pro Lys Leu Pro Pro 

Gly Glu Gln Cys Glu Gly Glu Glu Asp Thr Glu Phe Met Thr Pro Ser Ser Arg Pro Leu Arg Pro Leu Asp Thr Ser Gln Ser Ser Arg Ala Cys Asp Cys Asp Gln Gln Ile Asp Ser Cys Thr Tyr Glu Ala Met Tyr Asn Ile Gln Ser Gln Ala Pro Ser Ile Thr Glu Ser Ser Thr Phe Gly Glu Gly Asn Leu Ala Ala Ala His Ala Asn Thr Gly Pro Glu Glu Ser Glu Asn Glu Asp Asp Gly Tyr Asp Val Pro Lys Pro Pro Val Pro Ala Val Leu Ala Arg Arg Thr Leu Ser Asp Ile Ser Asn Ala Ser Ser Ser Phe Gly Trp Leu Ser Leu Asp Gly Asp Pro Thr Thr Asn Val Thr Glu Gly Ser Gln Val Pro Glu Arg Pro Pro Lys Pro Phe Pro Arg Arg Ile Asn Ser Glu Arg Lys Ala Gly Ser Cys Gln Gln Gly Ser Gly Pro Ala Ala Ser Ala Ala Thr Ala Ser Pro Gln Leu Ser Ser Glu Ile Glu Asn Leu Met Ser Gln Gly Tyr Ser Tyr Gln Asp Ile Gln Lys Ala Leu Val Ile Ala Gln Asn Asn Ile Glu Met Ala Lys Asn Ile Leu Arg Glu Phe Val 

Ser Ile Ser Ser Pro Ala His Val Ala Thr

<211> 2721 <212> DNA <213> Artificial <220> <223> c-Cbl Y731F <220> <221> CDS <222> (1)..(2718) <400> 255 atg gcc ggc aac gtg aag aag atc tct ggg gcc ggg ggc ggc acg ggc 48 Met Ala Gly Asn Val Lys Lys Ser Ser Gly Ala Gly Gly Thr Gly 10 tcc ggg ggc tcg ggt tcg ggt ggc ctg att ggg ctc atg aag gac gcc 96 Ser Gly Gly Ser Gly Ser Gly Leu Ile Gly Leu Met Lys Asp Ala 144 ttc cag ccg cac cac cac cac cac cac ctc agc ccc cac ccg ccg Phe Gln Pro His His His His His His Leu Ser Pro His Pro Pro 35 ggg acg gtg gac aag atg gtg gag aag tgc tgg aag ctc atg gac 192 Gly Thr Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp 50 55 240 aag gtg gtg cgg ttg tgt cag aac cca aag ctg gcg cta aag aat agc Lys Val Val Arg Leu Cys Gln Asn Pro Lys Leu Ala Leu Lys Asn Ser 70 75 cca cct tat atc tta gac ctg cta cca gat acc tac cag cat ctc cgt 288 Pro Pro Tyr Ile Leu Asp Leu Leu Pro Asp Thr Tyr Gln His Leu Arg 90 336 act atc ttg tca aga tat gag ggg aag atg gag aca ctt gga gaa aat Thr Ile Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn 100 105 384 Glu Tyr Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln 120 115 432 Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn 140 135 130 480 tct cag cct agg cga aac cta acc aaa ctg tcc ctc atc ttc agc cac Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His 160 145 150 atg ctg gca gaa cta aaa gga atc ttt cca agt gga ctc ttt cag gga 528 Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly 165

|   |     |     |     |     |     |     | aaa<br>Lys        |     |     |     |     |     |     |     |     |     | 576    |    |
|---|-----|-----|-----|-----|-----|-----|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|--------|----|
|   | _   |     |     | _   | _   |     | ata<br>Ile        | _   |     |     | _   | -   |     |     |     |     | 624    |    |
|   |     |     |     |     |     |     | atc<br>Ile<br>215 |     |     |     |     |     |     |     |     |     | 672    |    |
|   |     |     |     |     |     |     | acc<br>Thr        |     |     |     |     |     |     |     |     |     | 720    |    |
| • |     |     |     |     |     |     | ctc<br>Leu        |     |     |     |     |     |     |     |     |     | 768    |    |
|   |     |     |     |     |     |     | gta<br>Val        |     |     |     |     |     |     |     |     |     | 816    |    |
|   |     |     |     |     |     |     | gct<br>Ala        |     |     |     |     |     |     |     |     |     | 864    |    |
|   |     |     |     |     |     |     | ctg<br>Leu<br>295 |     |     |     |     |     |     |     |     |     | 912    |    |
|   |     |     |     |     |     |     | gat<br>Asp        |     |     |     |     |     |     |     |     |     | 960    | ·- |
|   |     |     |     |     |     |     | gca<br>Ala        |     |     |     |     |     |     |     |     |     | `1008  |    |
|   |     | _   |     |     | -   |     | cga<br>Arg        |     | _   |     |     |     |     |     |     |     | 1056   |    |
|   |     |     |     |     |     |     | gac<br>Asp        |     |     |     |     |     |     |     |     |     | ` 1104 |    |
|   | _   |     |     | _   |     | _   | ggc<br>Gly<br>375 |     |     |     |     |     | _   |     |     | _   | 1152   |    |
|   |     |     |     |     |     |     | gta<br>Val        |     |     |     |     |     |     |     |     |     | 1200   |    |
|   | tgc | aca | tcc | tgt | ctt | aca | tcc               | tgg | cag | gaa | tca | gaa | ggt | cag | ggc | tgt | 1248   |    |

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|   | Cys         | Thr | Ser | Cys | Leu<br>405 | Thr | Ser | Trp | Gln | Glu<br>410        | Ser | Glu | Gly | Gln | Gly<br>415 | Cys |      |  |  |
|---|-------------|-----|-----|-----|------------|-----|-----|-----|-----|-------------------|-----|-----|-----|-----|------------|-----|------|--|--|
|   |             |     |     |     |            |     |     |     |     | act<br>Thr        |     |     |     |     |            |     | 1296 |  |  |
|   |             |     |     |     |            |     |     |     |     | ctg<br>Leu        |     |     |     |     |            |     | 1344 |  |  |
|   |             |     |     |     |            | Asn |     |     |     | gat<br>Asp        |     |     |     |     |            |     | 1392 |  |  |
|   |             |     |     |     |            |     |     |     |     | gct<br>Ala        |     |     |     |     |            |     | 1440 |  |  |
|   |             |     |     |     |            |     |     |     |     | caa<br>Gln<br>490 |     |     |     |     |            |     | 1488 |  |  |
|   |             |     |     |     |            |     |     |     |     | cga<br>Arg        |     |     |     |     |            |     | 1536 |  |  |
|   | _           |     | _   |     |            |     | -   |     | -   | gct<br>Ala        | -   |     |     |     |            |     | 1584 |  |  |
|   |             |     |     |     |            |     |     |     |     | aca<br>Thr        |     |     |     |     |            |     | 1632 |  |  |
|   |             | _   |     |     | _          |     |     |     |     | gtt<br>Val        |     |     |     |     |            |     | 1680 |  |  |
| · | caa<br>.Gln |     |     |     |            |     |     |     |     | ggc<br>Gly<br>570 |     |     |     |     |            |     | 1728 |  |  |
|   |             |     |     |     |            |     |     |     |     | ctt<br>Leu        |     |     |     |     |            |     | 1776 |  |  |
|   |             |     |     |     |            |     |     |     |     | gcc<br>Ala        |     |     |     |     |            |     | 1824 |  |  |
|   |             |     |     |     |            |     |     |     |     | cac<br>His        |     |     |     |     |            |     | 1872 |  |  |
|   |             |     |     |     |            |     |     |     |     | gtg<br>Val        |     |     |     |     |            |     | 1920 |  |  |

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| 625   | 630 | 635                 | 640 |
|---|-----|---------------------|-----|
| ttc agt ctg gat acc<br>Phe Ser Leu Asp Thr<br>645 |     | n Ser Ser Pro Leu V |     |
| cca gag tgt gac cac<br>Pro Glu Cys Asp His<br>660 |     |                     |     |
| att tat tct ctg gct<br>Ile Tyr Ser Leu Ala<br>675 |     |                     |     |
| ggg gag caa tgt gag<br>Gly Glu Gln Cys Glu<br>690 |     |                     |     |
| tcc agg cct cta cgg<br>Ser Arg Pro Leu Arg<br>705 |     |                     |     |
| gat tgc gac cag cag<br>Asp Cys Asp Gln Gln<br>725 |     | r Phe Glu Ala Met T |     |
| att cag tcc cag gcg<br>Ile Gln Ser Gln Ala<br>740 |     |                     |     |
| ggg aat ttg gcc gca<br>Gly Asn Leu Ala Ala<br>755 |     |                     |     |
| aat gag gat gat ggg<br>Asn Glu Asp Asp Gly<br>770 |     |                     |     |
| ctg gcc cgc cga act<br>Leu Ala Arg Arg Thr<br>785 |     |                     |     |
| ggc tgg ttg tct ctg<br>Gly Trp Leu Ser Leu<br>805 |     | r Thr Asn Val Thr G |     |
| tcc caa gtt ccc gag<br>Ser Gln Val Pro Glu<br>820 |     |                     |     |
| tct gaa cgg aaa gct<br>Ser Glu Arg Lys Ala<br>835 |     |                     |     |
| tct gct gcc acc gcc<br>Ser Ala Ala Thr Ala<br>850 |     |                     |     |

| atg<br>Met<br>865            | agt<br>Ser   | cag<br>Gln                 | ggg<br>Gly        | tac<br>Tyr        | tcc<br>Ser<br>870 | tac<br>Tyr | cag<br>Gln | gac<br>Asp | atc<br>Ile        | cag<br>Gln<br>875 | aaa<br>Lys | gct<br>Ala | ttg<br>Leu | gtc<br>Val        | att<br>Ile<br>880 | 2640 |
|------------------------------|--------------|----------------------------|-------------------|-------------------|-------------------|------------|------------|------------|-------------------|-------------------|------------|------------|------------|-------------------|-------------------|------|
| gcc<br>Ala                   | cag<br>Gln   | aac<br>Asn                 | aac<br>Asn        | atc<br>Ile<br>885 | gag<br>Glu        | atg<br>Met | gcc<br>Ala | aaa<br>Lys | aac<br>Asn<br>890 | atc<br>Ile        | ctc<br>Leu | cgg<br>Arg | gaa<br>Glu | ttt<br>Phe<br>895 | gtt<br>Val        | 2688 |
|                              |              |                            | tct<br>Ser<br>900 |                   |                   |            |            |            |                   | tag               |            |            |            |                   |                   | 2721 |
| <210<br><211<br><212<br><213 | .> 9<br>!> I | 256<br>906<br>PRT<br>Artif | icia              | al                |                   |            |            |            |                   |                   |            |            |            |                   |                   |      |
| <220<br><223                 |              | Synth                      | netio             | c Cor             | nstru             | ıct        |            |            |                   |                   |            |            |            |                   |                   |      |
| <400                         | )> 2         | 256                        |                   |                   |                   |            |            |            |                   |                   |            |            |            |                   |                   |      |
| Met<br>1                     | Ala          | Gly                        | Asn               | Val<br>5          | Lys               | Lys        | Ser        | Ser        | Gly<br>10         | Ala               | Gly        | Gly        | Gly        | Thr<br>15         | Gly               |      |
| Ser                          | Gly          | Gly                        | Ser<br>20         | Gly               | Ser               | Gly        | Gly        | Leu<br>25  | Ile               | Gly               | Leu        | Meţ        | Lys<br>30  | Asp               | Ala               |      |
| Phe                          | Gln          | Pro<br>35                  | His               | His               | His               | His        | His<br>40  | His        | His               | Leu               | Ser        | Pro<br>45  | His        | Pro               | Pro               |      |
| Gly                          | Thr<br>50    | Val                        | Asp               | Lys               | Lys               | Met<br>55  | Val        | Glu        | Lys               | Cys               | Trp<br>60  | Lys        | Leu        | Met               | Asp               |      |
| Lys<br>65                    | Val          | Val                        | Arg               | Leu               | Cys<br>70         | Gln        | Asn        | Pro        | Lys               | Leu<br>75         | Ala        | Leu        | Lys        | Asn               | Ser<br>80         |      |
| Pro                          | Pro          | Tyr                        | Ile               | Leu<br>85         | Asp               | Leu        | Leu        | Pro        | Asp<br>90         | Thr               | Tyr        | Gln        | His        | Leu<br>95         | Arg               |      |
| Thr                          | Ile          | Leu                        | Ser<br>100        | Arg               | Tyr               | Glu        | Gly        | Lys<br>105 | Met               | Glu               | Thr        | Leu        | Gly<br>110 | Glu               | Asn               |      |
| Glu                          | Tyr          | Phe<br>115                 | Arg               | Val               | Phe               | Met        | Glu<br>120 | Asn        | Leu               | Met               | Lys        | Lys<br>125 | Thr        | Lys               | Gln               |      |
|                              |              |                            |                   |                   |                   |            |            |            |                   |                   |            |            |            | _                 |                   |      |

Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn

Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala Leu His Glu Val His Pro Ile Ser Ser Gly Leu Glu Ala Met Ala Leu . 215 Lys Ser Thr Ile Asp Leu Thr Cys Asn Asp Tyr Ile Ser Val Phe Glu Phe Asp Ile Phe Thr Arg Leu Phe Gln Pro Trp Ser Ser Leu Leu Arg Asn Trp Asn Ser Leu Ala Val Thr His Pro Gly Tyr Met Ala Phe Leu Thr Tyr Asp Glu Val Lys Ala Arg Leu Gln Lys Phe Ile His Lys Pro Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Glu Gln Tyr 

| Glu        | Leu<br>370 | Tyr        | Cys        | Glu        | Met        | Gly<br>375 | Ser        | Thr        | Phe        | Gln        | Leu<br>380 | Cys        | Lys        | Ile        | Cys        |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Ala<br>385 | Glu        | Asn        | Asp        | Lys        | Asp<br>390 | Val        | Lys        | Ile        | Glu        | Pro<br>395 | Cys        | Gly        | His        | Leu        | Met<br>400 |
| Cys        | Thr        | Ser        | Cys        | Leu<br>405 | Thr        | Ser        | Trp        | Gln        | Glu<br>410 | Ser        | Glu        | Gly        | Gln        | Gly<br>415 | Cys<br>,   |
| Pro        | Phe        | Cys        | Arg<br>420 | Cys        | Glu        | Ile        | Lys        | Gly<br>425 | Thr        | Glu        | Pro        | Ile        | Val<br>430 | Val        | Asp        |
| Pro        | Phe        | Asp<br>435 | Pro        | Arg        | Gly        | Ser        | Gly<br>440 | Ser        | Leu        | Leu        | Arg        | Gln<br>445 | Gly        | Ala        | Glu        |
| Gly        | Ala<br>450 | Pro        | Ser        | Pro        | Asn        | Tyr<br>455 | Asp        | Asp        | Asp        | Asp        | Asp<br>460 | Glu        | Arg        | Ala        | Asp        |
| Asp<br>465 | Thr        | Leu        | Phe        | Met        | Met<br>470 | Lys        | Glu        | Leu        | Ala        | Gly<br>475 | Ala        | Lys        | Val        | Glu        | Arg<br>480 |
| Pro        | Pro        | Ser        | Pro        | Phe<br>485 | Ser        | Met        | Ala        | Pro        | Gln<br>490 | Ala        | Ser        | Leu        | Pro        | Pro<br>495 | Val        |
| Pro        | Pro        | Arg        | Leu<br>500 | Asp        | Leu        | Leu<br>,   | Pro        | Gln<br>505 | Arg        | Val        | Cys        | Val        | Pro<br>510 | Ser        | Ser        |
| Ala        | Ser        | Ala<br>515 | Leu        | Gly        | Thr        | Ala        | Ser<br>520 | Lys        | Ala        | Ala        | Ser        | Gly<br>525 | Ser        | Leu        | His        |
| Lys        | Asp<br>530 | Lys        | Pro        | Leu        | Pro        | Val<br>535 | Pro        | Pro        | Thr        | Leu        | Arg<br>540 | Asp        | Leu        | Pro        | Pro        |
| Pro<br>545 | Pro        | Pro        | Pro        | Asp        | Arg<br>550 | Pro        | Tyŗ        | Ser        | Val        | Gly<br>555 | Ala        | Glu        | Ser        | Arg        | Pro<br>560 |
| Gln        | Arg        | Arg        | Pro        | Leu<br>565 | Pro        | Cys        | Thr        | Pro        | Gly<br>570 | Asp        | Cys        | Pro        | Ser        | Arg<br>575 | Asp        |
| Lys        | Leu        | Pro        | Pro<br>580 | Val        | Pro        | Ser        | Ser        | Arg<br>585 | Leu        | Gly        | Asp        | Ser        | Trp<br>590 | Leu        | Pro        |

| Arg        | Pro        | 595        | Pro        | гуs        | Val        | PIO        | 600        | ser        | Ala        | PIO        | ser        | 605        | ser        | Asp        | PIO .      |   |  |  |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|---|--|--|
| Trp        | Thr<br>610 | Gly        | Arg        | Glu        | Leu        | Thr<br>615 | Asn        | Arg        | His        | Ser        | Leu<br>620 | Pro        | Phe        | Ser        | Leu        |   |  |  |
| Pro<br>625 | Ser        | Gln        | Met        | Glu        | Pro<br>630 | Arg        | Pro        | Asp        | Val        | Pro<br>635 | Arg        | Leu        | Gly        | Ser        | Thr<br>640 |   |  |  |
| Phe        | Ser        | Leu        | Asp        | Thr<br>645 | Ser        | Met        | Ser        | Met        | Asn<br>650 | Ser        | Ser        | Pro        | Leu        | Val<br>655 | Gly.       |   |  |  |
| Pro        | Glu        | Cys        | Asp<br>660 | His        | Pro        | Lys        | Ile        | Lys<br>665 | Pro        | Ser        | Ser        | Ser        | Ala<br>670 | Asn        | Ala        |   |  |  |
| Ile        | Tyr        | Ser<br>675 | Leu        | Ala        | Ala        | Arg        | Pro<br>680 | Leu        | Pro        | Val        | Pro        | Lys<br>685 | Leu        | Pro        | Pro        |   |  |  |
| Gly        | Glu<br>690 | Gln        | Cys        | Glu<br>,   | Gly        | Glu<br>695 | Glu        | Asp        | Thr        | Glu        | Tyr<br>700 | Met        | Thr        | Pro        | Ser        |   |  |  |
| Ser<br>705 | Arg        | Pro        | Leu        | Arg        | Pro<br>710 | Leu        | Asp        | Thr        | Ser        | Gln<br>715 | Ser        | Ser        | Arg        | Ala        | Cys<br>720 |   |  |  |
| Asp        | Cys        | Asp        | Gln        | Gln<br>725 | Ile        | Asp        | Ser        | Cys        | Thr<br>730 | Phe        | Glu        | Ala        | Met        | Tyr<br>735 | Asn        |   |  |  |
| Ile        | Gln        | Ser        | Gln<br>740 | Ala        | Pro        | Ser        | Ile        | Thr<br>745 | Glu        | Ser        | Ser        | Thr        | Phe<br>750 | Gly        | Glu        | , |  |  |
| Gly        | Asn        | Leu<br>755 | Ala        | Ala        | Ala        | His        | Ala<br>760 | Asn        | Thr        | Gly        | Pro        | Glu<br>765 | Glu        | Ser        | Glu        |   |  |  |
| Asn        | Glu<br>770 | Asp        | Asp        | Gly        | Tyr        | Asp<br>775 | Val        | Pro        | Lys        | Pro        | Pro<br>780 | Val        | Pro        | Ala        | Val        |   |  |  |
| Leu<br>785 | Ala        | Arg        | Arg        | Thr        | Leu<br>790 | Ser        | Asp        | Ile        | Ser        | Asn<br>795 | Ala        | Ser        | Ser        | Ser        | Phe<br>800 |   |  |  |
| Gly        | Trp        | Leu        | Ser        | Leu<br>805 | Asp        | Gly        | Asp        | Pro        | Thr<br>810 | Thr        | Asn        | Val        | Thr        | Glu<br>815 | Gly        |   |  |  |

|                                 | •              |                      |                  |                 |            |            |                  |                  |                  |            |            |                  |                  |                  |            |     |  |
|---------------------------------|----------------|----------------------|------------------|-----------------|------------|------------|------------------|------------------|------------------|------------|------------|------------------|------------------|------------------|------------|-----|--|
|                                 |                |                      |                  |                 |            |            | •                |                  |                  |            |            |                  | •                | •                |            |     |  |
| Ser                             | Gln            | Val                  | Pro<br>820       | Glu             | Arg        | Pro        | Pro              | Lys<br>825       | Pro              | Phe        | Pro        | Arg              | Arg<br>830       | Ile              | Asn        |     |  |
| Ser                             | Glu            | Arg<br>835           | Lys              | Ala             | Gly        | Ser        | Cys<br>840       | Gln              | Gln              | Gly        | Ser        | Gly<br>845       | Pro              | Ala              | Ala        |     |  |
| Ser                             | Ala<br>850     |                      | . Thr            | Ala             | Ser        | Pro<br>855 | Gln              | Leu              | Ser              | Ser        | Glu<br>860 | Ile              | Glu              | Asn              | Leu        |     |  |
| Met<br>865                      |                | Glr                  | Gly              | Tyr             | Ser<br>870 | Tyr        | Gln              | Asp              | Ile              | Gln<br>875 | Lys        | Ala              | Leu              | Val              | Ile<br>880 |     |  |
| Ala                             | Glr            | ı Asr                | Asn              | Ile<br>885      | Glu        | Met        | Ala              | Lys              | Asn<br>890       | Ile        | Leu        | Arg              | Glu              | Phe<br>895       | Val        |     |  |
| Ser                             | Ιlε            | e Ser                | Ser<br>900       |                 | Ala        | His        | Val              | Ala<br>905       | Thr              |            |            |                  |                  |                  | -          |     |  |
| <21<br><21<br><21<br><22<br><22 | 2><br>3><br>0> |                      | fici<br>ol Y7    |                 |            |            |                  |                  |                  |            |            |                  |                  |                  |            |     |  |
|                                 | 3>             | c-Ch                 | ol Y7            | 74F             |            |            |                  |                  |                  |            |            |                  |                  |                  |            | ·   |  |
| <22<br><22                      |                | CDS (1)              | . (27            | 18)             |            |            |                  |                  |                  |            |            |                  |                  |                  |            |     |  |
| atg                             | gco            | 257<br>ggq<br>a Gly  | aac<br>Asn       | gtg<br>Val<br>5 | aag<br>Lys | aag<br>Lys | agc<br>Ser       | tct<br>Ser       | ggg<br>Gly<br>10 | gcc<br>Ala | Gly<br>ggg | ggc<br>Gly       | ggc<br>Gly       | acg<br>Thr<br>15 | ggc<br>Gly | 48  |  |
| tcc<br>Ser                      | ggg<br>Gly     | Gly<br>g ggd         | tcg<br>Ser<br>20 | ggt<br>Gly      | tcg<br>Ser | ggt<br>Gly | ggc<br>Gly       | ctg<br>Leu<br>25 | att<br>Ile       | ggg.       | ctc<br>Leu | atg<br>Met       | aag<br>Lys<br>30 | gac<br>Asp       | gcc<br>Ala | 96  |  |
| ttc                             | caç<br>Glı     | g ccg<br>n Pro<br>35 | g cac<br>His     | cac<br>His      | cac<br>His | cac<br>His | cac<br>His<br>40 | cac<br>His       | cac<br>His       | ctc<br>Leu | agc<br>Ser | ccc<br>Pro<br>45 | cac<br>His       | ccg<br>Pro       | ccg<br>Pro | 144 |  |
| Phe                             |                |                      | r gac            | aag             |            |            |                  |                  |                  |            | Trp        |                  |                  |                  |            | 192 |  |
| ggg                             |                |                      | . Asp            | Lys             | пуs        | 55         |                  |                  |                  |            | 60         |                  |                  |                  |            |     |  |

|   | cca        | cct               | tat               | atc               | tta        | gac        | ctg               | cta               | cca               | gat        | acc        | tac               | cag               | cat               | ctc               | cgt        | 288 |  |
|---|------------|-------------------|-------------------|-------------------|------------|------------|-------------------|-------------------|-------------------|------------|------------|-------------------|-------------------|-------------------|-------------------|------------|-----|--|
|   | Pro        | Pro               | Tyr               | Ile               | Leu<br>85  | Asp        | Leu               | Leu               | Pro               | Asp<br>90  | Thr        | Tyr               | Gln               | His               | Leu<br>95         | Arg        |     |  |
|   | act<br>Thr | atc<br>Ile        | ttg<br>Leu        | tca<br>Ser<br>100 | aga<br>Arg | tat<br>Tyr | gag<br>Glu        | ggg<br>Gly        | aag<br>Lys<br>105 | atg<br>Met | gag<br>Glu | aca<br>Thr        | ctt<br>Leu        | gga<br>Gly<br>110 | gaa<br>Glu        | aat<br>Asn | 336 |  |
|   |            |                   |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   | aag<br>Lys        |            | 384 |  |
|   |            |                   |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   | gag<br>Glu        |            | 432 |  |
|   |            |                   |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   | agc<br>Ser        |            | 480 |  |
| , | _          | _                 | _                 | _                 |            |            |                   |                   |                   |            | _          | -                 |                   |                   | cag<br>Gln<br>175 |            | 528 |  |
|   |            |                   |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   | aga<br>Arg        |            | 576 |  |
|   |            |                   |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   | cag<br>Gln        |            | 624 |  |
|   |            |                   |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   | gct<br>Ala        |            | 672 |  |
|   |            |                   |                   |                   | Asp        |            | Thr               | Cys               | Asn               | Asp        |            |                   |                   |                   | ttt<br>Phe        |            | 720 |  |
|   |            |                   |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   | ctc<br>Leu<br>255 |            | 768 |  |
|   |            |                   |                   |                   |            |            |                   |                   |                   |            |            |                   |                   |                   | ttt<br>Phe        |            | 816 |  |
|   | acg<br>Thr | tat<br>Tyr        | gac<br>Asp<br>275 | gaa<br>Glu        | gtg<br>Val | aaa<br>Lys | gct<br>Ala        | cgg<br>Arg<br>280 | ctc<br>Leu        | cag<br>Gln | aaa<br>Lys | ttc<br>Phe        | att<br>Ile<br>285 | cac<br>His        | aaa<br>Lys        | cct<br>Pro | 864 |  |
|   | ggc<br>Gly | agt<br>Ser<br>290 | tat<br>Tyr        | atc<br>Ile        | ttc<br>Phe | cgg<br>Arg | ctg<br>Leu<br>295 | agc<br>Ser        | tgt<br>Cys        | act<br>Thr | cgt<br>Arg | ctg<br>Leu<br>300 | ggt<br>Gly        | cag<br>Gln        | tgg<br>Trp        | gct<br>Ala | 912 |  |

| att gg<br>Ile Gl<br>305 | _      | -   |     | _   | -   |     |     |     |     | _   |     |     |     |     | 960  |
|-------------------------|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| aat aa<br>Asn Ly        |        |     |     |     |     |     |     | -   |     |     |     |     |     |     | 1008 |
| tat tt<br>Tyr Le        |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1056 |
| tgt ga<br>Cys Gl        |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1104 |
| gaa tt<br>Glu Le<br>37  | u Tyr  |     |     |     |     |     |     |     |     |     |     |     |     |     | 1152 |
| gct ga<br>Ala Gl<br>385 |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1200 |
| tgc ac                  |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1248 |
| cct tt<br>Pro Ph        |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1296 |
| ccg tt<br>Pro Ph        |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1344 |
| gga gc<br>Gly Al<br>45  | a Pro  |     |     |     |     |     |     |     |     |     |     |     |     |     | 1392 |
| gat ac<br>Asp Th<br>465 |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1440 |
| ccg cc<br>Pro Pr        |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1488 |
| cca co<br>Pro Pr        |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1536 |
| gct to<br>Ala Se        |        |     |     |     |     |     |     |     |     |     |     |     |     |     | 1584 |
| aaa ga                  | ac aaa | cca | ttg | cca | gta | cct | ccc | aca | ctt | cga | gat | ctt | cca | cca | 1632 |

| Lys        | Asp<br>530        | Lys        | Pro               | Leu        | Pro        | Val<br>535        | Pro        | Pro               | Thr        | Leu        | Arg<br>540        | Asp        | Leu               | Pro        | Pro        |        |
|------------|-------------------|------------|-------------------|------------|------------|-------------------|------------|-------------------|------------|------------|-------------------|------------|-------------------|------------|------------|--------|
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | tcc<br>Ser        |            |            | 1680   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | tcc<br>Ser        |            |            | 1728   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | tgg<br>Trp<br>590 |            |            | 1776   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | agt<br>Ser        |            |            | 1824   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | ttt<br>Phe        |            |            | 1872   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | gga<br>Gly        |            |            | 1920   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | tta<br>Leu        |            |            | 1968   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | gcc<br>Ala<br>670 |            |            | 2016   |
|            |                   |            | Leu               |            |            |                   |            |                   |            |            |                   |            | ctg<br>Leu        |            |            | 2064   |
| Gly<br>aaa | gag<br>Glu<br>690 | caa<br>Gln | tgt<br>Cys        | gag<br>Glu | ggt<br>Gly | gaa<br>Glu<br>695 | gag<br>Glu | gac<br>Asp        | aca<br>Thr | gag<br>Glu | tac<br>Tyr<br>700 | atg<br>Met | act<br>Thr        | ccc<br>Pro | tct<br>Ser | 2112   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | cga<br>Arg        |            |            | 2160   |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | atg<br>Met        |            |            | 2208   |
| att<br>Ile | cag<br>Gln        | tcc<br>Ser | cag<br>Gln<br>740 | gcg<br>Ala | cca<br>Pro | tct<br>Ser        | atc<br>Ile | acc<br>Thr<br>745 | gag<br>Glu | agc<br>Ser | agc<br>Ser        | acc<br>Thr | ttt<br>Phe<br>750 | ggt<br>Gly | gaa<br>Glu | 2256 . |
|            |                   |            |                   |            |            |                   |            |                   |            |            |                   |            | gag<br>Glu        |            |            | 2304   |

.

| 755 | 760 | 765 |
|-----|-----|-----|
|     |     |     |

|  |   |   | • |                   |   |  |     |   |   |  |      |
|--|---|---|---|-------------------|---|--|-----|---|---|--|------|
|  |   |   |   | ttt<br>Phe        |   |  |     |   |   |  | 2352 |
|  | _ | _ | _ | ctc<br>Leu<br>790 | _ |  |     | _ | - |  | 2400 |
|  |   |   |   | gat<br>Asp        |   |  |     |   |   |  | 2448 |
|  |   | _ |   | <br>agg<br>Arg    |   |  |     |   |   |  | 2496 |
|  |   |   |   | ggc<br>Gly        |   |  |     |   |   |  | 2544 |
|  |   |   |   | tca<br>Ser        |   |  |     |   |   |  | 2592 |
|  |   |   |   | tcc<br>Ser<br>870 |   |  |     |   |   |  | 2640 |
|  |   |   |   | gag<br>Glu        |   |  |     |   |   |  | 2688 |
|  |   |   |   | gcc<br>Ala        | - |  | tag |   |   |  | 2721 |
|  |   |   |   |                   |   |  |     |   |   |  |      |

<210> 258

<211> 906

<212> PRT

<213> Artificial

<220>

<223> Synthetic Construct

<400> 258

Met Ala Gly Asn Val Lys Lys Ser Ser Gly Ala Gly Gly Gly Thr Gly 1 5 10 15

Ser Gly Gly Ser Gly Ser Gly Gly Leu Ile Gly Leu Met Lys Asp Ala 20 25 30

| Pne        | GIN        | 35         | нıs        | HIS        | nis        | nis        | 40         | nis        | nis        | ьeu        | ser        | 45         | HIS        | PIO        | PIO        |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Gly        | Thr<br>50  | Val        | Asp        | Lys        | Lys        | Met<br>55  | Val        | Glu        | Lys        | Cys        | Trp<br>60  | Lys        | Leu        | Met        | Asp        |
| Lys<br>65  | Val        | Val        | Arg        | Leu        | Cys<br>70  | Gln        | Asn        | Pro        | Lys        | Leu<br>75  | Ala        | Leu        | Lys        | Asn        | Ser<br>80  |
| Pro        | Pro        | Tyr        | Ile        | Leu<br>85  | Asp        | Leu        | Leu        | Pro        | Asp<br>90  | Thr        | Tyr        | Gln        | His        | Leu<br>95  | Arg        |
| Thr        | Ile        | Leu        | Ser<br>100 | Arg        | Tyr        | Glu        | Gly        | Lys<br>105 | Met        | Glu        | Thr        | Leu        | Gly<br>110 | Glu        | Asn        |
| Glu        | Tyr        | Phe<br>115 | Arg        | Val        | Phe        | Met        | Glu<br>120 | Asn        | Leu        | Met        | Lys        | Lys<br>125 | Thr        | Lys        | Gln        |
| Thr        | Ile<br>130 | Ser        | Leu        | Phe        | Lys        | Glu<br>135 | Gly        | Lys        | Glu        | Arg        | Met<br>140 | Tyr        | Glu        | Glu        | Asn        |
| Ser<br>145 | Gln        | Pro        | Arg        | Arg        | Asn<br>150 | Leu        | Thr        | Lys        | Leu        | Ser<br>155 | Leu        | Ile        | Phe        | Ser        | His<br>160 |
| Met        | Leu        | Ala        | Glu        | Leu<br>165 | Lys        | Gly        | Ile        | Phe        | Pro<br>170 | Ser        | Gly        | Leu        | Phe        | Gln<br>175 | Gly        |
| Asp        | Thr        | Phe        | Arg<br>180 | Ile        | Thr        | Lys        | Ala        | Asp<br>185 | Ala        | Ala        | Glu        | Phe        | Trp<br>190 | Arg        | Lys        |
| Ala        | Phe        | Gly<br>195 | Glu        | Lys        | Thr        | Ile        | Val<br>200 | Pro        | Trp        | Lys        | Ser        | Phe<br>205 | Arg        | Gln        | Ala        |
| Leu        | His<br>210 | Glu        | Val        | His        | Pro        | Ile<br>215 | Ser        | Ser        | Gly        | Leu        | Glu<br>220 | Ala        | Met        | Ala        | Leu        |
| Lys<br>225 | Ser        | Thr        | Ile        | Asp        | Leu<br>230 | Thr        | Cys        | Asn        | Asp        | Tyr<br>235 | Ile        | Ser        | Val        | Phe        | Glu<br>240 |
| Phe        | Asp        | Ile        | Phe        | Thr<br>245 | Arg        | Leu        | Phe        | Gln        | Pro<br>250 | Trp        | Ser        | Ser        | Leu        | Leu<br>255 | Arg        |
| Asn        | Trp        | Asn        | Ser        | Leu        | Ala        | Val        | Thr        | His        | Pro        | Gly        | Tyr        | Met        | Ala        | Phe        | Leu        |

260 265 270

| Thr        | Tyr        | Asp<br>275 | Glu        | Val        | Lys        | Ala        | Arg<br>280 | Leu        | Gln        | Lys         | Phe        | Ile<br>285 | His        | Lys        | Pro        |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------|------------|------------|------------|------------|------------|
| Gly        | Ser<br>290 | Tyr        | Ile        | Phe        | Arg        | Leu<br>295 | Ser        | Cys        | Thr        | Arg         | Leu<br>300 | Gly        | Gln        | Trp        | Ala        |
| Ile<br>305 | Gly        | Tyr        | Val        | Thr        | Ala<br>310 | Asp        | Gly        | Asn        | Ile        | Leu<br>315  | Gln        | Thr        | Ile        | Pro        | His<br>320 |
| Asn        | Lys        | Pro        | Leu        | Phe<br>325 | Gln        | Ala        | Leu        | Ile        | Asp<br>330 | Gly         | Phe        | Arg        | Glu        | Gly<br>335 | Phe        |
| Tyr        | Leu        | Phe        | Pro<br>340 | Asp        | Gly        | Arg        | Asn        | Gln<br>345 | Asn        | Pro         | Asp        | Leu        | Thr<br>350 | Gly        | Leu        |
| Cys        | Glu        | Pro<br>355 | Thr        | Pro        | Gln        | Asp        | His<br>360 | Ile        | Lys        | Val         | Thr        | Gln<br>365 | Glu        | Gln        | Туг        |
| Glu        | Leu<br>370 | Tyr        | Cys        | Glu        | Met        | Gly<br>375 | Ser        | Thr        | Phe        | Gln         | Leu<br>380 | Cys        | Lys        | Ile        | Суз        |
| Ala<br>385 | Glu        | Asn        | Asp        | Lys        | Asp<br>390 | Val        | Lys        | Ile        | Glu        | Pro<br>395  | Cys        | Gly        | His        | Leu        | Met<br>400 |
| Cys        | Thr        | Ser        | Cys        | Leu<br>405 | Thr        | Ser        | Trp        | Gln        | Glu<br>410 | Ser         | Glu        | Gly        | Gln        | Gly<br>415 |            |
| Pro        | Phe        | Cys        | Arg<br>420 | Cys        | Glu        | Ile        | Lys        | Gly<br>425 | Thr        | Glu         | Pro        | Ile        | Val<br>430 | Val        | Ası        |
| Pro        | Phe        | Asp<br>435 | Pro        | Arg        | Gly        | Ser        | Gly<br>440 | Ser        | Leu        | Leu<br>•    | Arg        | Gln<br>445 | Gly        | Ala        | Glu        |
| Gly        | Ala<br>450 | Pro        | Ser        | Pro        | Asn        | Tyr<br>455 | Asp        | Asp        | Asp        | Asp         | Asp<br>460 | Glu        | Arg        | Ala        | Asp        |
| Asp<br>465 | Thr        | Leu        | Phe        | Met        | Met<br>470 | Lys        | Glu        | Leu        | Ala        | Gly<br>475. |            | Lys        | Val        | Glu        | Arg<br>480 |
| Pro        | Pro        | Ser        | Pro        | Phe<br>485 | Ser        | Met        | Ala        | Pro        | Gln<br>490 | Ala         | Ser        | Leu        | Pro        | Pro<br>495 | Va]        |

| Pro        | Pro        | Arg        | Leu<br>500 | Asp        | Leu        | Leu        | Pro        | Gln<br>505 | Arg        | Val        | Cys        | Val        | Pro<br>510 | Ser        | Ser        |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Ala        | Ser        | Ala<br>515 | Leu        | Gly        | Thr        | Ala        | Ser<br>520 | Lys        | Ala        | Ala        | Ser        | Gly<br>525 | Ser        | Leu        | His        |
| Lys        | Asp<br>530 | Lys        | Pro        | Leu        | Pro        | Val<br>535 | Pro        | Pro        | Thr        | Leu        | Arg<br>540 | Asp        | Leu        | Pro        | Pro        |
| Pro<br>545 | Pro        | Pro        | Pro        | Asp        | Arg<br>550 | Pro        | Tyr        | Ser        | Val        | Gly<br>555 | Ala        | Glu        | Ser        | Arg        | Pro<br>560 |
| Gln        | Arg        | Arg        | Pro        | Leu<br>565 | Pro        | Cys        | Thr        | Pro        | Gly<br>570 | Asp        | Cys        | Pro        | Ser        | Arg<br>575 | Asp        |
| Lys        | Leu        | Pro        | Pro<br>580 | Val        | Pro        | Ser        | Ser        | Arg<br>585 | Leu        | Gly        | Asp        | Ser        | Trp<br>590 | Leu        | Pro        |
| Arg        | Pro        | Ile<br>595 | Pro        | Lys        | Val        | Pro        | Val<br>600 | Ser        | Ala        | Pro        | Ser        | Ser<br>605 | Ser        | Asp        | Pro        |
| Trp        | Thr<br>610 | Gly        | Arg        | Glu        | Leu        | Thr<br>615 | Asn        | Arg        | His        | Ser        | Leu<br>620 | Pro        | Phe        | Ser        | Leu        |
| Pro<br>625 | Ser        | Gln        | Met        | Glu        | Pro<br>630 | Arg        | Pro        | Asp        | Val        | Pro<br>635 | Arg        | Leu        | Gly        | Ser        | Thr<br>640 |
| Phe        | Ser        | Leu        | Asp        | Thr<br>645 | Ser        | Met        | Ser        | Met        | Asn<br>650 | Ser        | Ser        | Pro        | Leu        | Val<br>655 | Gly        |
| Pro        | Glu        | Cys        | Asp<br>660 | His        | Pro        | Lys        | Ile        | Lys<br>665 | Pro        | Ser        | Ser        | Ser        | Ala<br>670 | Asn        | Ala        |
| Ile        | Tyr        | Ser<br>675 | Leu        | Ála        | Ala        | Arg        | Pro<br>680 | Leu        | Pro        | Val        | Pro        | Lys<br>685 | Leu        | Pro        | Pro        |
| Gly        | Glu<br>690 | Gln        | Cys        | Glu        | Gly        | Glu<br>695 | Glu        | Asp        | Thr        | Glu        | Tyr<br>700 | Met        | Thr        | Pro        | Ser        |
| Ser<br>705 | Arg        | Pro        | Leu        | Arg        | Pro<br>710 | Leu        | Asp        | Thr        | Ser        | Gln<br>715 | Ser        | Ser        | Arg        | Ala        | Cys<br>720 |

•

Asp Cys Asp Gln Gln Ile Asp Ser Cys Thr Tyr Glu Ala Met Tyr Asn 725 730 735

Ile Gln Ser Gln Ala Pro Ser Ile Thr Glu Ser Ser Thr Phe Gly Glu 740 745 750

Gly Asn Leu Ala Ala Ala His Ala Asn Thr Gly Pro Glu Glu Ser Glu 755 760 765

Asn Glu Asp Asp Gly Phe Asp Val Pro Lys Pro Pro Val Pro Ala Val 770 775 780

Leu Ala Arg Arg Thr Leu Ser Asp Ile Ser Asn Ala Ser Ser Ser Phe 785 790 . 795 800

Gly Trp Leu Ser Leu Asp Gly Asp Pro Thr Thr Asn Val Thr Glu Gly 805 810 815

Ser Gln Val Pro Glu Arg Pro Pro Lys Pro Phe Pro Arg Arg Ile Asn 820 825 830

Ser Glu Arg Lys Ala Gly Ser Cys Gln Gln Gly Ser Gly Pro Ala Ala 835 840 845

Ser Ala Ala Thr Ala Ser Pro Gln Leu Ser Ser Glu Ile Glu Asn Leu 850 855 860

Met Ser Gln Gly Tyr Ser Tyr Gln Asp Ile Gln Lys Ala Leu Val Ile 865 870 875 880

Ala Gln Asn Asn Ile Glu Met Ala Lys Asn Ile Leu Arg Glu Phe Val 885 890 895

Ser Ile Ser Ser Pro Ala His Val Ala Thr 900 905

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|            |            | _          |                   |            |            | atc<br>Ile<br>215 | -          |                   |            | _          |            |            |                   |            |            | 672  |  |
|------------|------------|------------|-------------------|------------|------------|-------------------|------------|-------------------|------------|------------|------------|------------|-------------------|------------|------------|------|--|
|            |            |            |                   |            |            | acc<br>Thr        |            |                   |            |            |            |            |                   |            |            | 720  |  |
|            |            |            |                   |            |            | ctc<br>Leu        |            |                   |            |            |            |            |                   |            |            | 768  |  |
|            |            |            |                   |            |            | gta<br>Val        |            |                   |            |            |            |            |                   |            |            | 816  |  |
|            |            |            |                   |            |            | gct<br>Ala        |            |                   |            |            |            |            |                   |            |            | 864  |  |
|            |            |            |                   |            |            | ctg<br>Leu<br>295 |            |                   |            |            |            |            |                   |            |            | 912  |  |
|            |            |            |                   |            |            | gat<br>Asp        |            |                   |            |            |            |            |                   |            |            | 960  |  |
|            |            |            |                   |            |            | gca<br>Ala        |            |                   |            |            |            |            |                   |            |            | 1008 |  |
|            |            |            |                   |            |            | cga<br>Arg        |            |                   |            |            |            |            |                   |            |            | 1056 |  |
|            |            |            |                   |            |            | gac<br>Asp        |            |                   |            |            |            |            |                   |            |            | 1104 |  |
|            |            |            |                   |            |            | ggc<br>Gly<br>375 |            |                   |            |            |            |            |                   |            |            | 1152 |  |
|            |            |            |                   |            |            | gta<br>Val        |            |                   |            |            |            |            |                   |            |            | 1200 |  |
|            |            |            |                   |            |            | tcc<br>Ser        |            |                   |            |            |            |            |                   |            |            | 1248 |  |
| cct<br>Pro | ttc<br>Phe | tgc<br>Cys | cga<br>Arg<br>420 | tgt<br>Cys | gaa<br>Glu | att<br>Ile        | aaa<br>Lys | ggt<br>Gly<br>425 | act<br>Thr | gaa<br>Glu | ccc<br>Pro | atc<br>Ile | gtg<br>Val<br>430 | gta<br>Val | gat<br>Asp | 1296 |  |

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|            |            |            |            |                   |            | agt<br>Ser        |            |            |                   |            |            |            |            |                   |            | 1344 |
|------------|------------|------------|------------|-------------------|------------|-------------------|------------|------------|-------------------|------------|------------|------------|------------|-------------------|------------|------|
|            |            |            |            |                   |            | tat<br>Tyr<br>455 |            |            |                   |            |            |            |            |                   |            | 1392 |
|            |            |            |            |                   |            | aag<br>Lys        |            |            |                   |            |            |            |            |                   |            | 1440 |
|            |            |            |            |                   |            | atg<br>Met        |            |            |                   |            |            |            |            |                   |            | 1488 |
|            |            |            |            |                   |            | ctg<br>Leu        |            |            |                   |            |            |            |            |                   |            | 1536 |
|            |            |            |            |                   |            | gct<br>Ala        |            |            |                   |            |            |            |            |                   |            | 1584 |
|            |            |            |            |                   |            | gta<br>Val<br>535 |            |            |                   |            |            |            |            |                   |            | 1632 |
|            |            |            |            |                   |            | cca<br>Pro        |            |            |                   |            |            |            |            |                   |            | 1680 |
| caa<br>Gln | aga<br>Arg | cgc<br>Arg | ccc<br>Pro | ttg<br>Leu<br>565 | cct<br>Pro | tgt<br>Cys        | aca<br>Thr | cca<br>Pro | ggc<br>Gly<br>570 | gac<br>Asp | tgt<br>Cys | ccc<br>Pro | tcc<br>Ser | aga<br>Arg<br>575 | gac<br>Asp | 1728 |
|            |            |            |            |                   |            | tct<br>Ser        |            |            |                   |            |            |            |            |                   |            | 1776 |
|            |            |            |            |                   |            | cca<br>Pro        |            |            |                   |            |            |            |            |                   |            | 1824 |
|            |            |            |            |                   |            | acc<br>Thr<br>615 |            |            |                   |            |            |            |            |                   |            | 1872 |
|            |            |            |            |                   |            | aga<br>Arg        |            |            |                   |            |            |            |            |                   |            | 1920 |
|            |            |            |            |                   |            | atg<br>Met        |            |            |                   |            |            |            |            |                   |            | 1968 |
| cca        | gag        | tgt        | gac        | cac               | ccc        | aaa               | atc        | aaa        | cct               | tcc        | tca        | tct        | gcc        | aat               | gcc        | 2016 |

| Pro               | Glu               | Суѕ               | Asp<br>660 | His               | Pro               | Lys               | Ile               | Lys<br>665        | Pro               | Ser               | Ser               | Ser               | Ala<br>670 | Asn               | Ala               |      |   |
|-------------------|-------------------|-------------------|------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------|-------------------|-------------------|------|---|
|                   |                   |                   |            |                   |                   |                   |                   | ctt<br>Leu        |                   |                   |                   |                   |            |                   |                   | 2064 |   |
| Gly               | gag<br>Glu<br>690 | caa<br>Gln        | tgt<br>Cys | gag<br>Glu        | ggt<br>Gly        | gaa<br>Glu<br>695 | gag<br>Glu        | gac<br>Asp        | aca<br>Thr        | gag<br>Glu        | ttc<br>Phe<br>700 | atg<br>Met        | act<br>Thr | ccc<br>Pro        | tct<br>Ser        | 2112 |   |
|                   |                   |                   |            |                   |                   |                   |                   | aca<br>Thr        |                   |                   |                   |                   |            |                   |                   | 2160 |   |
|                   |                   |                   |            |                   |                   |                   |                   | tgt<br>Cys        |                   |                   |                   |                   |            |                   |                   | 2208 |   |
|                   |                   |                   |            |                   |                   |                   |                   | acc<br>Thr<br>745 |                   |                   |                   |                   |            |                   |                   | 2256 |   |
|                   |                   |                   |            |                   |                   |                   |                   | aac<br>Asn        |                   |                   |                   |                   |            |                   |                   | 2304 |   |
|                   |                   |                   |            |                   |                   |                   |                   | cca<br>Pro        |                   |                   |                   |                   |            |                   |                   | 2352 |   |
| ctg<br>Leu<br>785 | gcc<br>Ala        | cgc<br>Arg        | cga<br>Arg | act<br>Thr        | ctc<br>Leu<br>790 | tca<br>Ser        | gat<br>Asp        | atc<br>Ile        | tct<br>Ser        | aat<br>Asn<br>795 | gcc<br>Ala        | agc<br>Ser        | tcc<br>Ser | tcc<br>Ser        | ttt<br>Phe<br>800 | 2400 | · |
| ggc<br>Gly        | tgg<br>Trp        | ttg<br>Leu        | tct<br>Ser | ctg<br>Leu<br>805 | gat<br>Asp        | ggt<br>Gly        | gat<br>Asp        | cct<br>Pro        | aca<br>Thr<br>810 | aca<br>Thr        | aat<br>Asn        | gtc<br>Val        | act<br>Thr | gaa<br>Glu<br>815 | ggt<br>Gly        | 2448 |   |
|                   |                   |                   |            |                   |                   |                   |                   | aaa<br>Lys<br>825 |                   |                   |                   |                   |            |                   |                   | 2496 |   |
| tct<br>Ser        | gaa<br>Glu        | cgg<br>Arg<br>835 | aaa<br>Lys | gct<br>Ala        | ggc<br>Gly        | agc<br>Ser        | tgt<br>Cys<br>840 | cag<br>Gln        | caa<br>Gln        | ggt<br>Gly        | agt<br>Ser        | ggt<br>Gly<br>845 | cct<br>Pro | gcc<br>Ala        | gcc<br>Ala        | 2544 |   |
| tct<br>Ser        | gct<br>Ala<br>850 | gcc<br>Ala        | acc<br>Thr | gcc<br>Ala        | tca<br>Ser        | cct<br>Pro<br>855 | cag<br>Gln        | ctc<br>Leu        | tcc<br>Ser        | agt<br>Ser        | gag<br>Glu<br>860 | atc<br>Ile        | gag<br>Glu | aac<br>Asn        | ctc<br>Leu        | 2592 |   |
| atg<br>Met<br>865 | agt<br>Ser        | cag<br>Gln        | ggg<br>Gly | tac<br>Tyr        | tcc<br>Ser<br>870 | tac<br>Tyr        | cag<br>Gln        | gac<br>Asp        | atc<br>Ile        | cag<br>Gln<br>875 | aaa<br>Lys        | gct<br>Ala        | ttg<br>Leu | gtc<br>Val        | att<br>Ile<br>880 | 2640 |   |
| gcc<br>Ala        | cag<br>Gln        | aac<br>Asn        | aac<br>Asn | atc<br>Ile        | gag<br>Glu        | atg<br>Met        | gcc<br>Ala        | aaa<br>Lys        | aac<br>Asn        | atc<br>Ile        | ctc<br>Leu        | cgg<br>Arg        | gaa<br>Glu | ttt<br>Phe        | gtt<br>Val        | 2688 |   |

tcc att tct tct cct gcc cat gta gct acc tag Ser Ile Ser Ser Pro Ala His Val Ala Thr 900

2721

<210> 260

<211> 906

<212> PRT

<213> Artificial

<220>

<223> Synthetic Construct

<400> 260

Met Ala Gly Asn Val Lys Lys Ser Ser Gly Ala Gly Gly Thr Gly 5

Ser Gly Gly Ser Gly Ser Gly Leu Ile Gly Leu Met Lys Asp Ala 25 20

Phe Gln Pro His His His His His His Leu Ser Pro His Pro Pro 40

Gly Thr Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp 60

Lys Val Val Arg Leu Cys Gln Asn Pro Lys Leu Ala Leu Lys Asn Ser 70 65

Pro Pro Tyr Ile Leu Asp Leu Pro Asp Thr Tyr Gln His Leu Arg 90 85

Thr Ile Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn 105 100

Glu Tyr Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln 120

Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn 130 135

Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His 150 155 145

Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly 165 170 175

Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys 180 185 190

Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala 195 200 205

Leu His Glu Val His Pro Ile Ser Ser Gly Leu Glu Ala Met Ala Leu 210 215 .220

Lys Ser Thr Ile Asp Leu Thr Cys Asn Asp Tyr Ile Ser Val Phe Glu 225 230 235 240

Phe Asp Ile Phe Thr Arg Leu Phe Gln Pro Trp Ser Ser Leu Leu Arg 245 250 255

Asn Trp Asn Ser Leu Ala Val Thr His Pro Gly Tyr Met Ala Phe Leu 260 265 270

Thr Tyr Asp Glu Val Lys Ala Arg Leu Gln Lys Phe Ile His Lys Pro 275 280 285

Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala 290 295 300

Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His 305 310 315

Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe 325 330 335

Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu 340 345 350

Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Glu Gln Tyr 355 360 365

Glu Leu Tyr Cys Glu Met Gly Ser Thr Phe Gln Leu Cys Lys Ile Cys 370 375 380

Ala Glu Asn Asp Lys Asp Val Lys Ile Glu Pro Cys Gly His Leu Met

Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu 435 440 445

Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Glu Arg Ala Asp 450 460

Asp Thr Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg 465 470 475 480

Pro Pro Ser Pro Phe Ser Met Ala Pro Gln Ala Ser Leu Pro Pro Val 485 490 495

Pro Pro Arg Leu Asp Leu Leu Pro Gln Arg Val Cys Val Pro Ser Ser .500 505 510

Ala Ser Ala Leu Gly Thr Ala Ser Lys Ala Ala Ser Gly Ser Leu His 515 520 525

Lys Asp Lys Pro Leu Pro Val Pro Pro Thr Leu Arg Asp Leu Pro Pro 530 540

Pro Pro Pro Pro Asp Arg Pro Tyr Ser Val Gly Ala Glu Ser Arg Pro 545 550 555 560

Gln Arg Arg Pro Leu Pro Cys Thr Pro Gly Asp Cys Pro Ser Arg Asp 565 570 575

Lys Leu Pro Pro Val Pro Ser Ser Arg Leu Gly Asp Ser Trp Leu Pro 580 585 590

Arg Pro Ile Pro Lys Val Pro Val Ser Ala Pro Ser Ser Ser Asp Pro 595 600 605

Trp Thr Gly Arg Glu Leu Thr Asn Arg His Ser Leu Pro Phe Ser Leu 610 615 620

| Pro<br>625 | Ser        | Gln        | Met        | Glu        | Pro<br>630 | Arg        | Pro        | Asp        | Val        | Pro<br>635 | Arg        | Leu        | Gly        | Ser        | Thr<br>640 |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Phe        | Ser        | Leu        | Asp        | Thr<br>645 | Ser        | Met        | Ser        | Met        | Asn<br>650 | Ser        | Ser        | Pro        | Leu        | Val<br>655 | Gly        |
| Pro        | Glu        | Cys        | Asp<br>660 | His        | Pro        | Lys        | Ile        | Lys<br>665 | Pro        | Ser        | Ser        | Ser        | Ala<br>670 | Asn        | Ala        |
| Ile        | Tyr        | Ser<br>675 | Leu        | Ala        | Ala        | Arg        | Pro<br>680 | Leu        | Pro        | Val        | Pro        | Lys<br>685 | Leu        | Pro        | Pro        |
| Gly        | Glu<br>690 | Gln        | Суѕ        | Glu        | Gly        | Glu<br>695 | Glu        | Asp        | Thr        | Glu        | Phe<br>700 | Met        | Thr        | Pro        | Ser        |
| Ser<br>705 | Arg        | Pro        | Leu        | Arg        | Pro<br>710 | Leu        | Asp        | Thr        | Ser        | Gln<br>715 | Ser        | Ser        | Arg        | Ala        | Cys<br>720 |
| Asp        | Cys        | Asp        | Gln        | Gln<br>725 | Ile        | Asp        | Ser        | Cys        | Thr<br>730 | Phe        | Glu        | Ala        | Met        | Tyr<br>735 | Asn        |
| Ile        | Gln        | Ser        | Gln<br>740 | Ala        | Pro        | Ser        | Ile        | Thr<br>745 | Glu        | Ser        | Ser        | Thr        | Phe<br>750 | Gly        | Glu        |
| Gly        | Asn        | Leu<br>755 | Ala        | Ala        | Ala        | His        | Ala<br>760 | Asn        | Thr        | Gly        | Pro        | Glu<br>765 | Glu        | Ser        | Glu        |
| Asn        | Gļu<br>770 | Asp        | Asp        | Gly        | Phe        | Asp<br>775 | Val        | Pro        | Lys        | Pro        | Pro<br>780 | Val        | Pro        | Ala        | Val        |
| Leu<br>785 | Ala        | Arg        | Arg        | Thr        | Leu<br>790 | Ser        | Asp        | Ile        | Ser        | Asn<br>795 | Ala        | Ser        | Ser        | Ser        | Phe<br>800 |
| Gly        | Trp        | Leu        | Ser        | Leu<br>805 | Asp        | Gly        | Asp        | Pro        | Thr<br>810 | Thr        | Asn        | Val        | Thr        | Glu<br>815 | Gly        |
| Ser        | Gln        | Val        | Pro<br>820 | Glu        | Arg        | Pro        | Pro        | Lys<br>825 | Pro        | Phe        | Pro        | Arg        | Arg<br>830 | Ile        | Asn        |
| Ser        | Glu        | Arg<br>835 | Lys        | Ala        | Gly        | Ser        | Cys<br>840 | Gln        | Gln        | Gly        | Ser        | Gly<br>845 | Pro        | Ala        | Ala        |

| Ser Ala Ala<br>850                                  | Thr Ala Ser        | Pro Gln Leu<br>855               | Ser Ser Glu<br>860 |         | Asn Leu        |
|---|--------------------|----------------------------------|--------------------|---------|----------------|
| Met Ser Gln<br>865                                  | Gly Tyr Ser<br>870 | Tyr Gln Asp                      | lle Gln Lys<br>875 | Ala Leu | Val Ile<br>880 |
| Ala Gln Asn   | Asn Ile Glu<br>885 | Met Ala Lys                      | Asn Ile Leu<br>890 |         | Phe Val<br>895 |
| Ser Ile Ser   | Ser Pro Ala        | His Val Ala                      |                    |         |                |
| <210> 261<br><211> 1443<br><212> DNA<br><213> Artis | ficial             |                                  |                    |         |                |
| <220><br><223> c-Cb                                 | 1 480              |                                  |                    |         |                |
| <220> <221> CDS <222> (1).                          | . (1440)           |                                  | •                  |         |                |
|   |                    | aag agc tct<br>Lys Ser Ser       |                    | Gly Gly |                |
|   |                    | ggt ggc ctg<br>Gly Gly Leu<br>25 |                    |         |                |
|   |                    | cac cac cac<br>His His His       |                    |         |                |
|   |                    | atg gtg gag<br>Met Val Glu<br>55 |                    |         |                |
|   |                    | cag aac cca<br>Gln Asn Pro       |                    |         |                |
|   |                    | ctg cta cca<br>Leu Leu Pro       |                    | Gln His |                |
|   |                    | gag ggg aag<br>Glu Gly Lys       |                    |         |                |

100 105 110

|   |   |   |   | gtg<br>Val        |   |  |  |  |  |  | 384  |
|---|---|---|---|-------------------|---|--|--|--|--|--|------|
|   |   |   |   | ttc<br>Phe        |   |  |  |  |  |  | 432  |
|   |   |   |   | cga<br>Arg        |   |  |  |  |  |  | 480  |
|   |   |   |   | cta<br>Leu<br>165 |   |  |  |  |  |  | 528  |
|   |   |   |   | att<br>Ile        |   |  |  |  |  |  | 576  |
| _ |   |   | _ | aag<br>Lys        |   |  |  |  |  |  | 624  |
|   |   | _ | - | cat<br>His        |   |  |  |  |  |  | 672  |
|   |   |   |   | gat<br>Asp        |   |  |  |  |  |  | 720  |
|   | _ |   |   | acc<br>Thr<br>245 | - |  |  |  |  |  | 768  |
|   |   |   |   | ctt<br>Leu        |   |  |  |  |  |  | 816  |
|   |   |   |   | gtg<br>Val        |   |  |  |  |  |  | 864  |
|   |   |   |   | ttc<br>Phe        |   |  |  |  |  |  | 912  |
|   |   |   |   | act<br>Thr        |   |  |  |  |  |  | 960  |
|   |   |   |   | ttc<br>Phe<br>325 |   |  |  |  |  |  | 1008 |

| tat ttg<br>Tyr Leu        | Phe Pi                       | _           |       | -   |     | _   |           |     | -   | -   |     | -         |     | 1056 |
|---------------------------|------------------------------|-------------|-------|-----|-----|-----|-----------|-----|-----|-----|-----|-----------|-----|------|
| tgt gaa<br>Cys Glu        |                              |             |       | -   |     |     |           |     |     | _   | _   |           |     | 1104 |
| gaa tta<br>Glu Leu<br>370 | -                            |             |       |     |     |     |           |     |     | _   |     |           | -   | 1152 |
| gct gaa<br>Ala Glu<br>385 |                              |             |       |     |     |     |           |     |     |     |     |           |     | 1200 |
| tgc aca<br>Cys Thr        | _                            | _           |       |     |     | _   | _         |     | _   |     |     |           | -   | 1248 |
| cct ttc<br>Pro Phe        | Cys A                        |             | _     |     |     |     |           | -   |     |     |     |           |     | 1296 |
| ccg ttt<br>Pro Phe        | _                            | -           |       | _   |     | _   | _         | _   |     |     |     | -         |     | 1344 |
| gga gct<br>Gly Ala<br>450 |                              |             |       |     | -   | -   | _         | _   | _   | -   |     |           |     | 1392 |
| gat act<br>Asp Thr<br>465 |                              | -           | _     | _   | _   | _   | _         |     | _   | -   |     | _         |     | 1440 |
| tag                       |                              |             |       |     |     |     |           |     |     |     | •   |           |     | 1443 |
| <211> 4<br><212> H        | 262<br>180<br>PRT<br>Artific | cial        |       |     |     |     |           |     |     |     |     |           |     |      |
| <220><br><223>            | Synthet                      | cic Co      | nstru | ıct |     |     |           |     |     |     |     |           |     |      |
| <400> 2                   | 262                          |             |       |     |     |     |           |     |     |     |     |           |     |      |
| Met Ala<br>1              | Gly As                       | sn Val<br>5 | Lys   | Lys | Ser | Ser | Gly<br>10 | Ala | Gly | Gly | Gly | Thr<br>15 | Gly |      |

Ser Gly Gly Ser Gly Ser Gly Gly Leu Ile Gly Leu Met Lys Asp Ala 20  $\phantom{\bigg|}25\phantom{\bigg|}30\phantom{\bigg|}$ 

Phe Gln Pro His His His His His His Leu Ser Pro His Pro Pro Gly Thr Val Asp Lys Lys Met Val Glu Lys Cys Trp Lys Leu Met Asp Lys Val Val Arg Leu Cys Gln Asn Pro Lys Leu Ala Leu Lys Asn Ser Pro Pro Tyr Ile Leu Asp Leu Leu Pro Asp Thr Tyr Gln His Leu Arg Thr Ile Leu Ser Arg Tyr Glu Gly Lys Met Glu Thr Leu Gly Glu Asn Glu Tyr Phe Arg Val Phe Met Glu Asn Leu Met Lys Lys Thr Lys Gln Thr Ile Ser Leu Phe Lys Glu Gly Lys Glu Arg Met Tyr Glu Glu Asn Ser Gln Pro Arg Arg Asn Leu Thr Lys Leu Ser Leu Ile Phe Ser His Met Leu Ala Glu Leu Lys Gly Ile Phe Pro Ser Gly Leu Phe Gln Gly 165 · Asp Thr Phe Arg Ile Thr Lys Ala Asp Ala Ala Glu Phe Trp Arg Lys Ala Phe Gly Glu Lys Thr Ile Val Pro Trp Lys Ser Phe Arg Gln Ala Leu His Glu Val His Pro Ile Ser Ser Gly Leu Glu Ala Met Ala Leu Lys Ser Thr Ile Asp Leu Thr Cys Asn Asp Tyr Ile Ser Val Phe Glu Phe Asp Ile Phe Thr Arg Leu Phe Gln Pro Trp Ser Ser Leu Leu Arg 

Asn Trp Asn Ser Leu Ala Val Thr His Pro Gly Tyr Met Ala Phe Leu Thr Tyr Asp Glu Val Lys Ala Arg Leu Gln Lys Phe Ile His Lys Pro Gly Ser Tyr Ile Phe Arg Leu Ser Cys Thr Arg Leu Gly Gln Trp Ala Ile Gly Tyr Val Thr Ala Asp Gly Asn Ile Leu Gln Thr Ile Pro His Asn Lys Pro Leu Phe Gln Ala Leu Ile Asp Gly Phe Arg Glu Gly Phe Tyr Leu Phe Pro Asp Gly Arg Asn Gln Asn Pro Asp Leu Thr Gly Leu Cys Glu Pro Thr Pro Gln Asp His Ile Lys Val Thr Gln Glu Gln Tyr Glu Leu Tyr Cys Glu Met Gly Ser Thr Phe Gln Leu Cys Lys Ile Cys Ala Glu Asn Asp Lys Asp Val Lys Ile Glu Pro Cys Gly His Leu Met Cys Thr Ser Cys Leu Thr Ser Trp Gln Glu Ser Glu Gly Gln Gly Cys Pro Phe Cys Arg Cys Glu Ile Lys Gly Thr Glu Pro Ile Val Val Asp Pro Phe Asp Pro Arg Gly Ser Gly Ser Leu Leu Arg Gln Gly Ala Glu Gly Ala Pro Ser Pro Asn Tyr Asp Asp Asp Asp Glu Arg Ala Asp Asp Thr Leu Phe Met Met Lys Glu Leu Ala Gly Ala Lys Val Glu Arg 

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<220>

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| <220><br><223> | synthetic oligonucleotide probe for detecting mouse coca                                 | ine- and  |
|----------------|--|-----------|
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| tccttc         | tcgt gggacgcatc atccacggca gagtagatgt ccagg  | 45        |
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\* •